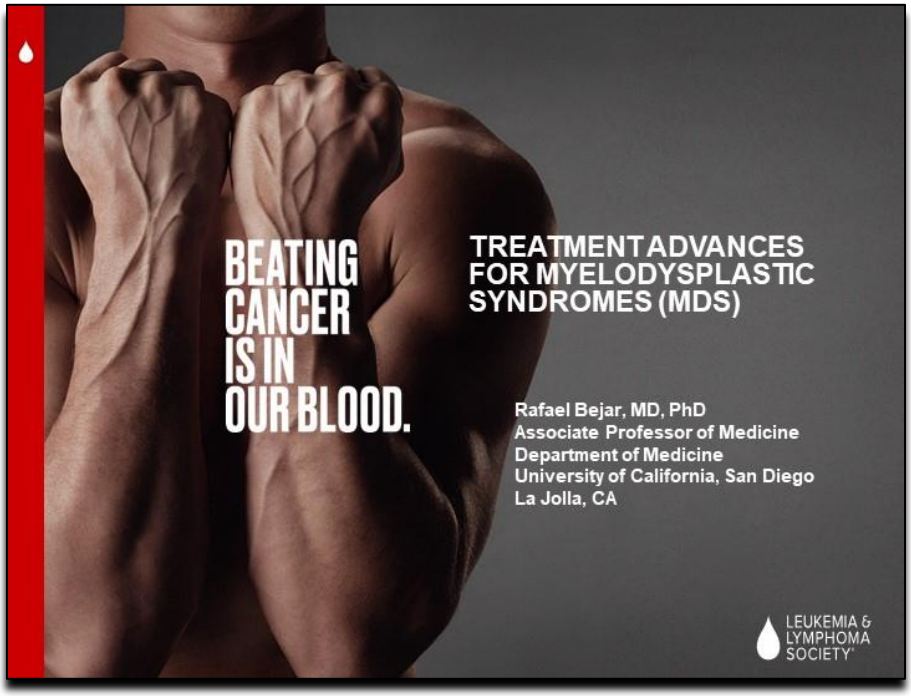


Welcome and Introductions: Treatment Advances for Myelodysplastic Syndromes

Operator:
Greetings, and welcome to Treatment Advances for Myelodysplastic Syndromes (MDS) on a live telephone and web education program. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you, Ms. Figueroa-Rivera. You may begin.

Ms. Lizette Figueroa-Rivera
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Before we begin, our President and CEO, Louis DeGennaro, would like to make some remarks.

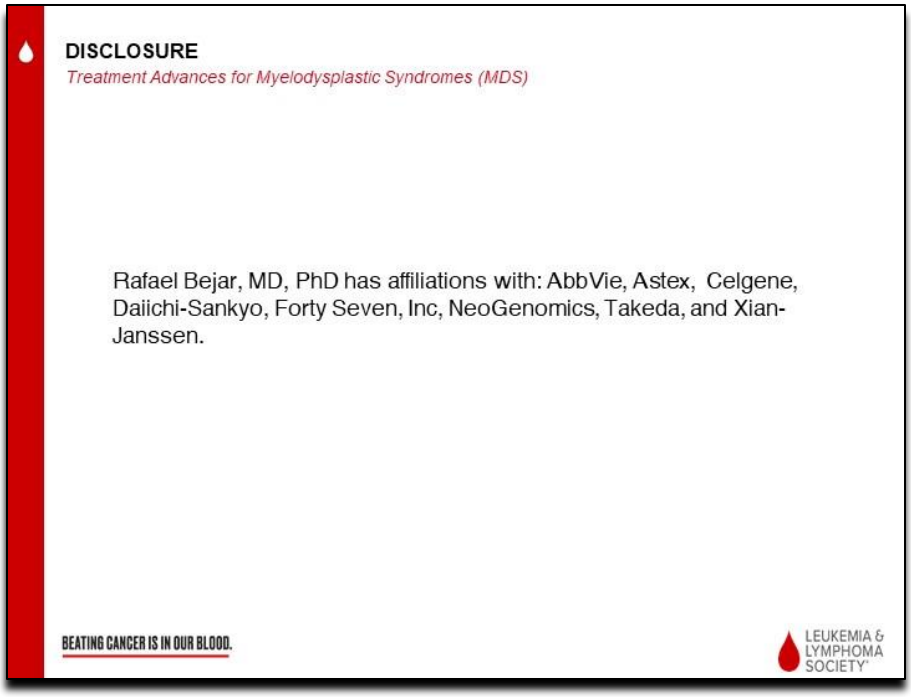
Dr. Louis DeGennaro
I'm Dr. Louis DeGennaro, President and CEO of The Leukemia & Lymphoma Society. I'd like to welcome all of the patients, caregivers, and health care professionals attending the program today. At The Leukemia & Lymphoma Society, our vision is a world without blood cancers. Since we started in 1949, LLS has invested more than $1.2 billion in breakthrough research to advance lifesaving treatments and cures.

We've played a pioneering role in funding many of today's most promising advances, including targeted therapies and immunotherapies that have led to increased survival rates and improved the quality of life for many blood cancer patients.

Though LLS is known for funding groundbreaking research, we do so much more. As this program demonstrates, we are the leading source of free blood cancer information, education, and support for patients, survivors, caregivers, families, and health care professionals.

We also support blood cancer patients in their local communities through our chapters across the country. And we advocate at the state and federal level for policies to ensure that patients have access to quality, affordable, and coordinated care. We're committed to working tirelessly toward our mission every single day.

Today, you'll have the opportunity to learn from esteemed key opinion leaders. They each have volunteered their time, and we appreciate their dedication to supporting our mission—their commitment to caring for patients living with blood cancers. Thank you for joining us.



Disclosure Slide

Ms. Lizette Figueroa-Rivera
Thank you. We would like to acknowledge and thank Bristol-Myers Squibb and Takeda Oncology for support of this program.

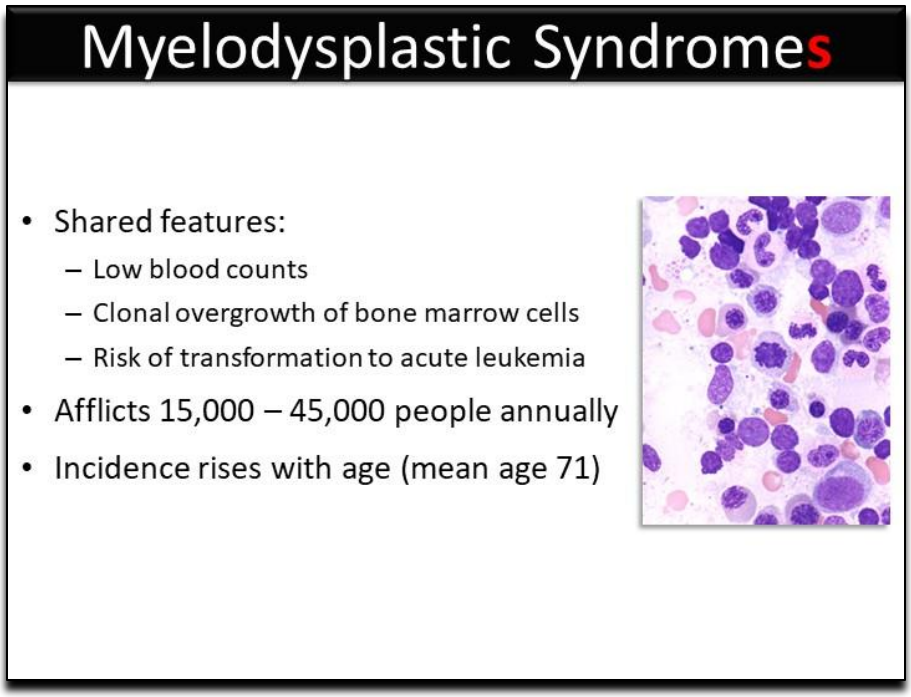
Treatment Advances for Myelodysplastic Syndromes (MDS)

I am now pleased to introduce Dr. Rafael Bejar, Associate Professor of Medicine, Department of Medicine, at the University of California, San Diego, in La Jolla, California. On behalf of The Leukemia & Lymphoma Society, thank you so much for volunteering your time and expertise with us. Dr. Bejar, I am now privileged to turn the program over to you.

Overview

Rafael Bejar, MD, PhD
Thank you, Lizette. Really appreciate you all being here and the LLS for supporting this educational program. I'm going to be speaking today about myelodysplastic syndromes, starting with some basic information and background just to make sure that we're all on the same page. I'll talk about what MDS is, how we diagnose it [and] classify it, and—importantly—assess risk in patients who have this disorder.

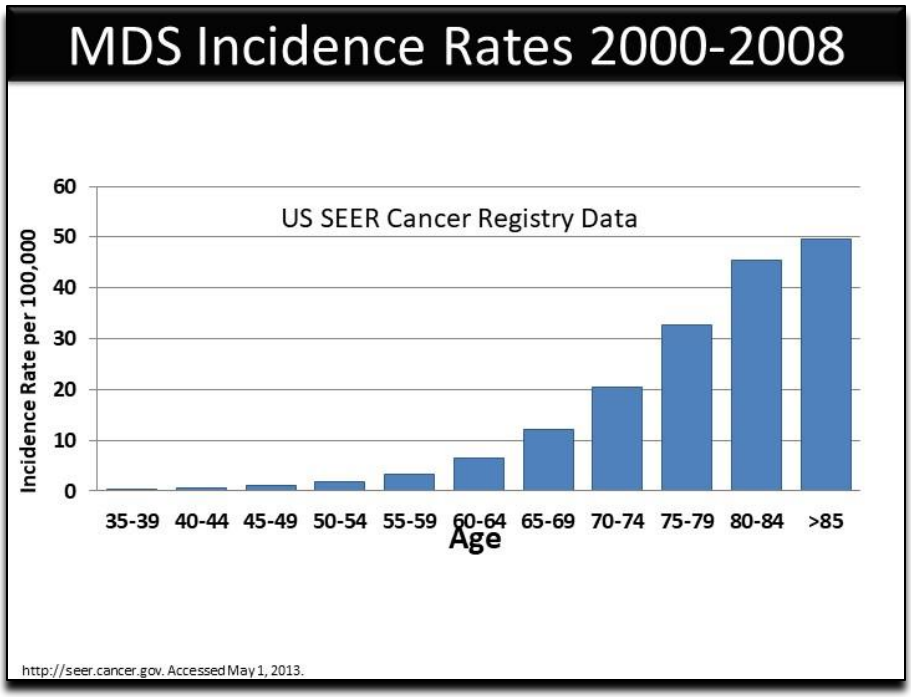
Finally, we'll spend a lot of time focusing on treatments, both for lower risk MDS and for higher risk MDS, including some new and emerging therapies that were recently updated on at the Annual [American] Society of Hematology (ASH) Meeting in Orlando just last week. We'll have plenty of time for questions and answers as well, and I hope that you find this program helpful, educational—and shed light on new topics in MDS.



Myelodysplastic Syndromes

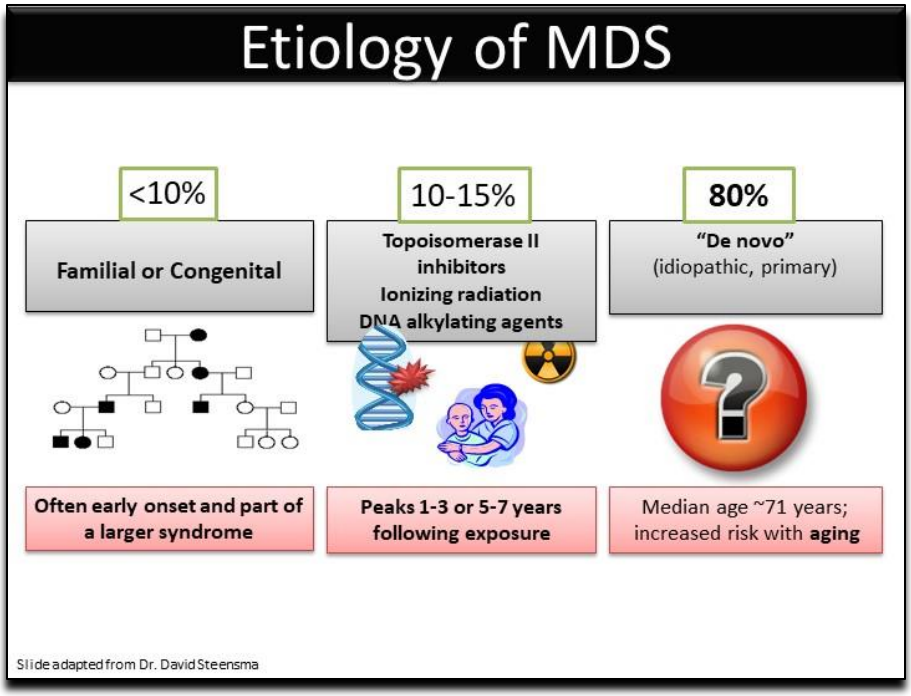
So, to start with I always show this slide that has the "S" in myelodysplastic syndromes highlighted in red. It just reminds me that this is not really one disorder. It's a collection of disorders that share some common features. And those features are low blood counts; a clonal outgrowth of bone marrow cells, which I'll explain in greater detail in a moment; and unfortunately, the risk of this disease turning into a more aggressive cancer called acute leukemia.

It's not actually very rare, even though most of us don't necessarily know someone else with this disorder. But it affects about 15,000 to 45,000 people annually, and it's primarily a disease associated with aging.



MDS Incidence Rates: 2000-2008

As you see in this next slide, the rate of MDS in the population goes up quite substantially after about the age of 60, with about 50 cases at 100,000 for patients that are over the age of 80.



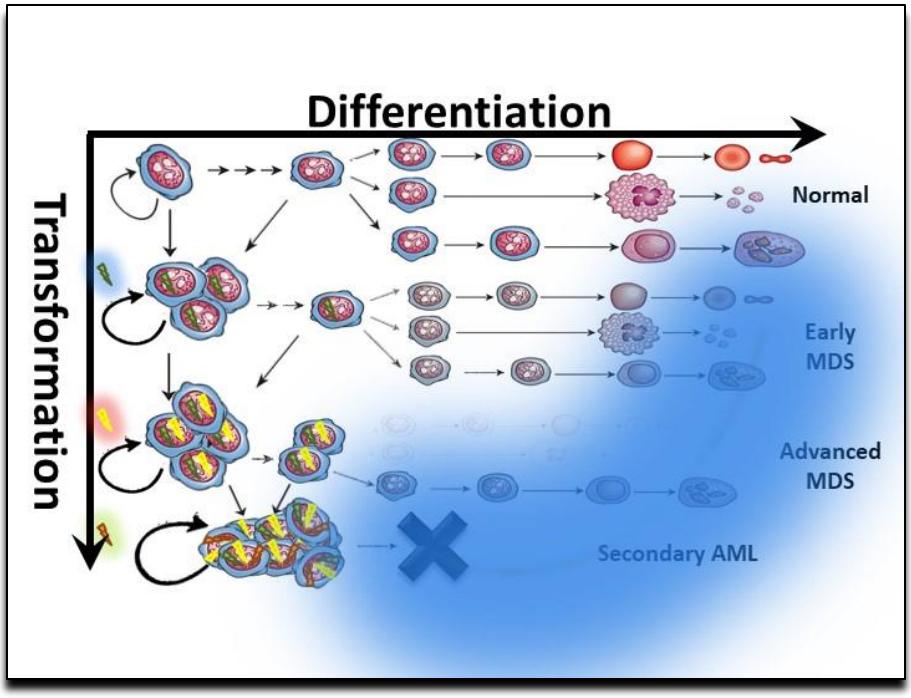
Etiology of MDS

Now, a question that I often get is, "Why do people get MDS?" If we think about what causes the disease and we look at individual patients, we find that about 10% of patients or so may have some family history of this disorder, and there may be some genetic predisposition to get this disease.

When this happens, it often occurs earlier in life or is part of a larger syndrome that can be recognized either in childhood or in early adulthood. However, we're starting to learn that certain genetic predispositions may not show up until patients are in their 60s or 70s, so it's another area of MDS research that I think is going to be changing how we look at this disease in the future.

Then there are a population of patients who have this disease as a consequence of prior treatment, presumably for another cancer where they received chemotherapy or radiation that might have led to the outgrowth of abnormal blood cells. Now, this usually occurs shortly after exposure, but the risk continues lifelong.

For most patients, unfortunately, we don't have a clear explanation for why they got MDS. It isn't necessarily something they were exposed to or something they were born with. This is just something that just occurred over their lifetime. And the major risk factor that we're aware of is aging.



Differentiation

Now, to think about why MDS occurs and where it occurs, I want to show you this diagram that starts with a cell in the upper left-hand corner there that's a hematopoietic stem cell. This cell has this unique ability to self-renew, meaning that when it divides, instead of turning into a more mature cell, it makes a perfect copy of itself.

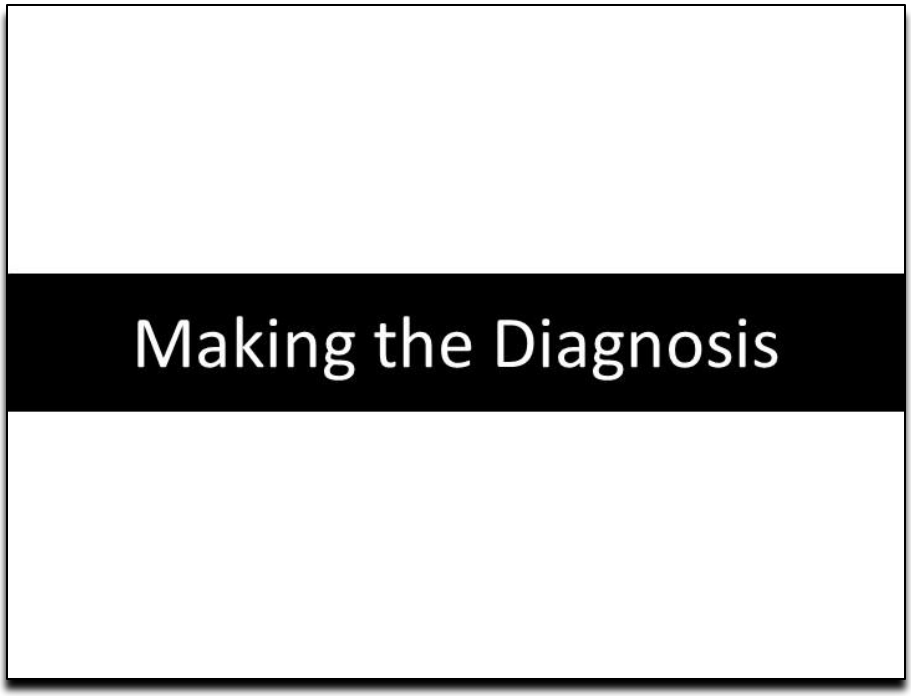
This is an important feature for our stem cells because we want to have them throughout our entire life. We want to replenish them when we use them. But the stem cells can also turn into more mature cells that go on to make all of the cells in our bloodstream. And they have a very careful balance between self-renewal and differentiation or maturation into normal blood cells.

In MDS, this balance is disrupted. And it's disrupted because of the mutation that occurs in that stem cell. That stem cell now behaves differently than it should. It starts to either grow or expand more than it should, and it begins to crowd out normal stem cells.

Now, these stem cells in MDS still retain the ability to turn into mature blood cells. They just do it less efficiently. So, they make fewer of these cells or make cells that are abnormal and don't live quite as long.

And this genetic damage that I talked about is not a single event. It's really multiple events that occur over a period of time. And more mutations can accumulate. And unfortunately, as more mutations occur, it becomes more difficult for that abnormal bone marrow to make mature blood cells.

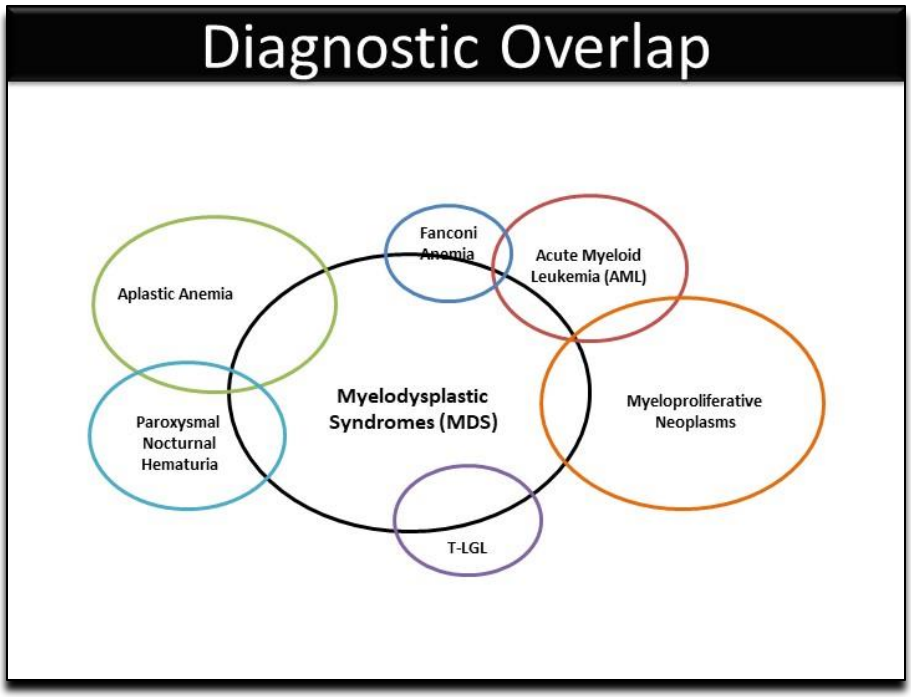
At some point when we have so many primitive cells that have stopped differentiating or maturing, they begin to accumulate in the bone marrow as cells that we call blasts. We no longer call the disease MDS. Now we call it AML—or acute myeloid leukemia—that has occurred after MDS.



Making the Diagnosis

Now I, in my research life, study how these mutations affect this disease. However, in my clinical life as a physician who treats patients with MDS—know that the major symptoms that people suffer are a consequence of the low blood counts—these low hemoglobin counts, low platelet counts, and low neutrophil counts that affect multiple aspects of their life.

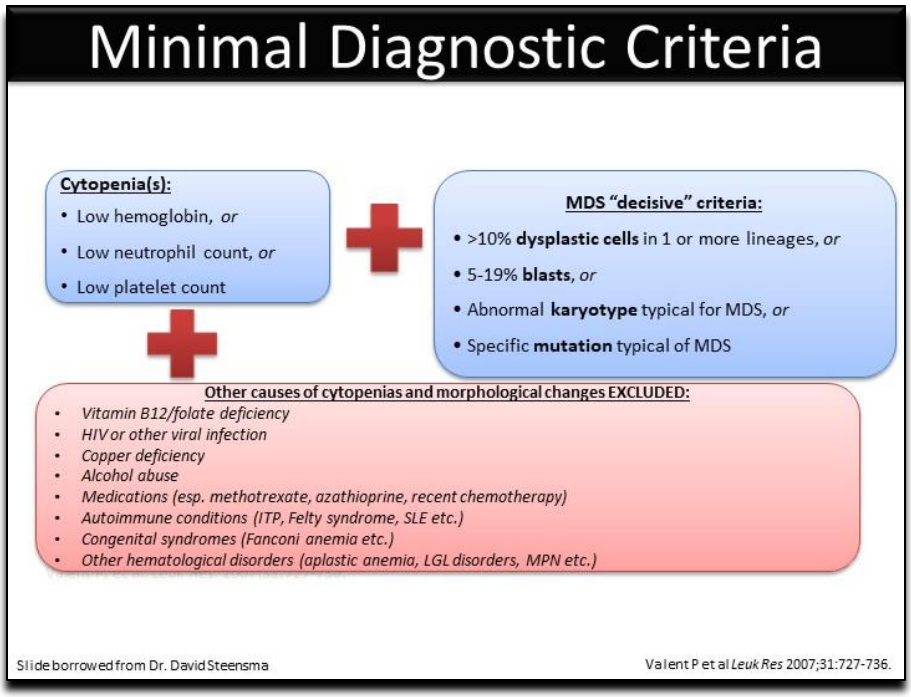
So, you'll see when we talk about treatment, we're going to focus not only on treatments that can kill the abnormal cells but on treatments that might help us extract a few more normal cells out of those mutated MDS cells.



Diagnostic Overlap

So, let me start with what I do in clinic when I see a patient that I suspect might have MDS. Making the diagnosis of MDS is not often straightforward. Some patients may have other conditions that could contribute to the low blood counts, and we need to make sure that we're talking about the right diagnosis.

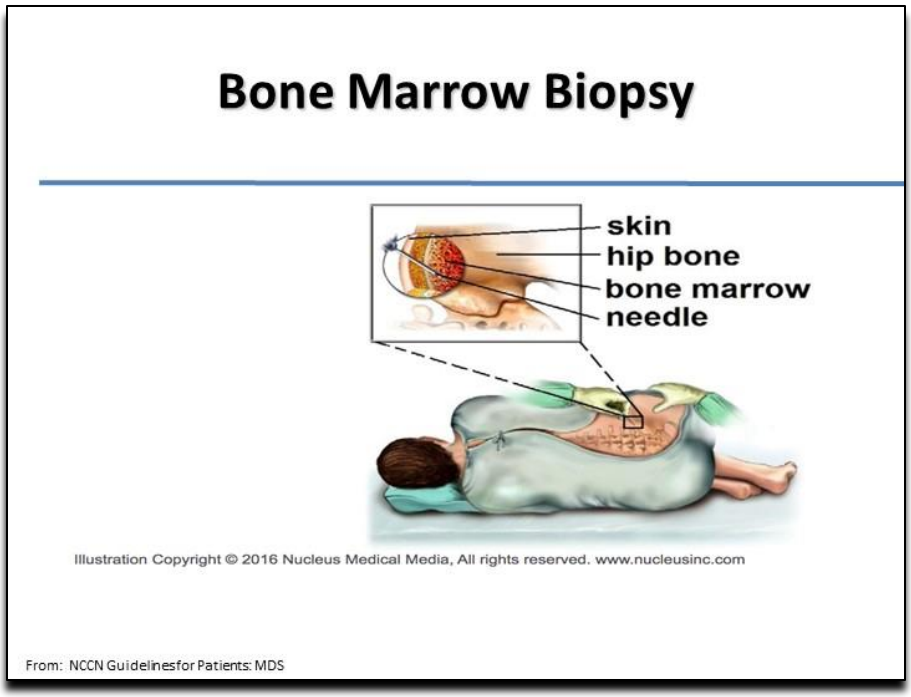
There also are a constellation of diagnoses that resemble MDS or [that] MDS mimics. That could be aplastic anemia or other disorders, like myeloproliferative neoplasms like myelofibrosis. Even acute leukemia can sometimes look like MDS at first. So, we spend a lot of time trying to make sure that we have the right disorder, so we can treat it appropriately.



Minimal Diagnostic Criteria

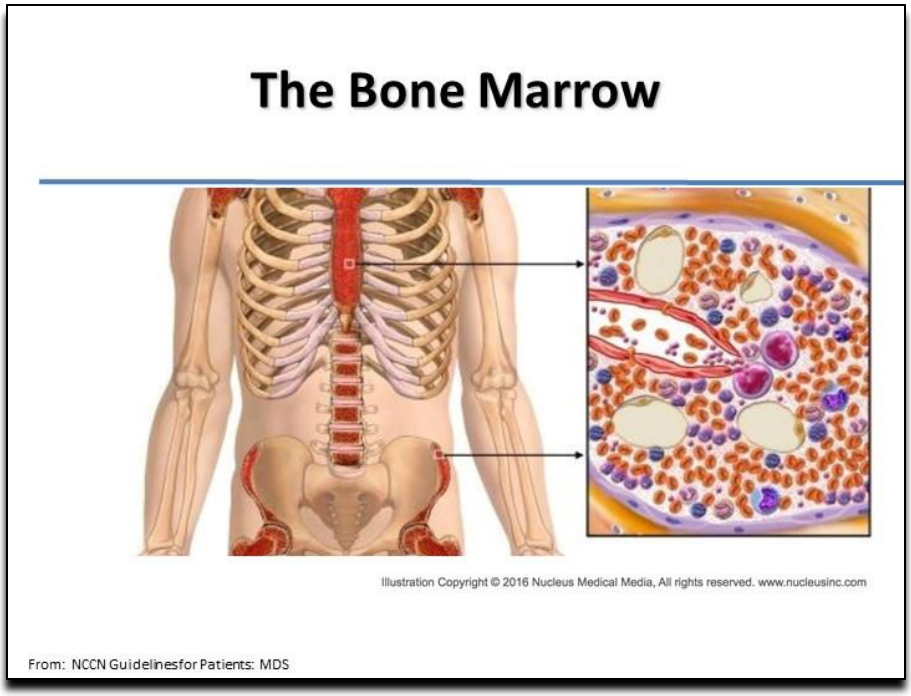
The criteria for diagnosing MDS include having a low blood count—either a low hemoglobin neutrophil count or platelet count—and having an abnormal finding in the bone marrow. And this can be more than 10% of cells look abnormal or have dysplasia, one of the defining characteristics of MDS. It can be the presence of 5% up to 19% blasts. When the blasts are greater than 20%, then we call the disease acute myeloid leukemia.

And finally, as I'll show you, we can look at the chromosomes. And if the chromosomes are abnormal in a way that is typical for MDS, we can use that as evidence that the disease is there. However, even that is not enough. We also need to look to see that we don't have any other disorders that could be contributing to the low blood counts that we're seeing to make sure that we identify them, as many of these are more easily treated than MDS itself. This includes vitamin deficiencies, mineral deficiencies, the presence of certain viral infections, many medications that can affect the bone marrow, autoimmune conditions, and so on.



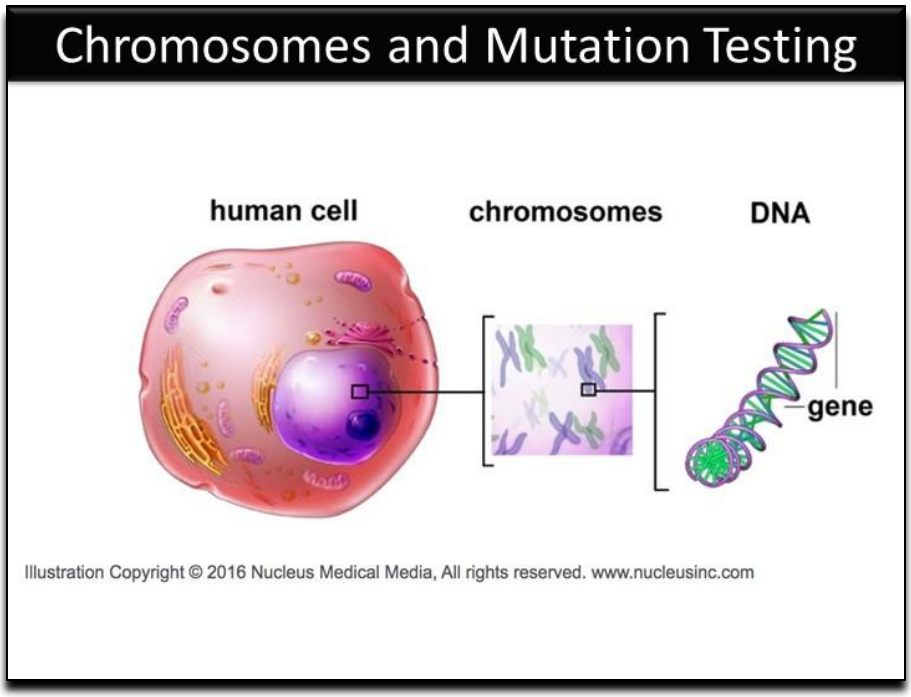
Bone Marrow Biopsy

So, your doctor will do a variety of studies to try to identify whether MDS is present, the most important of which is a bone marrow biopsy. This is a small sample of the bone marrow that's usually collected from the pelvis.



The Bone Marrow

This sample will give us information that allows us to diagnose the disease because we can see the blood cells in their factory: in the bone marrow. Next to each other, we can understand the relationships. And we can see if any of them are abnormal.

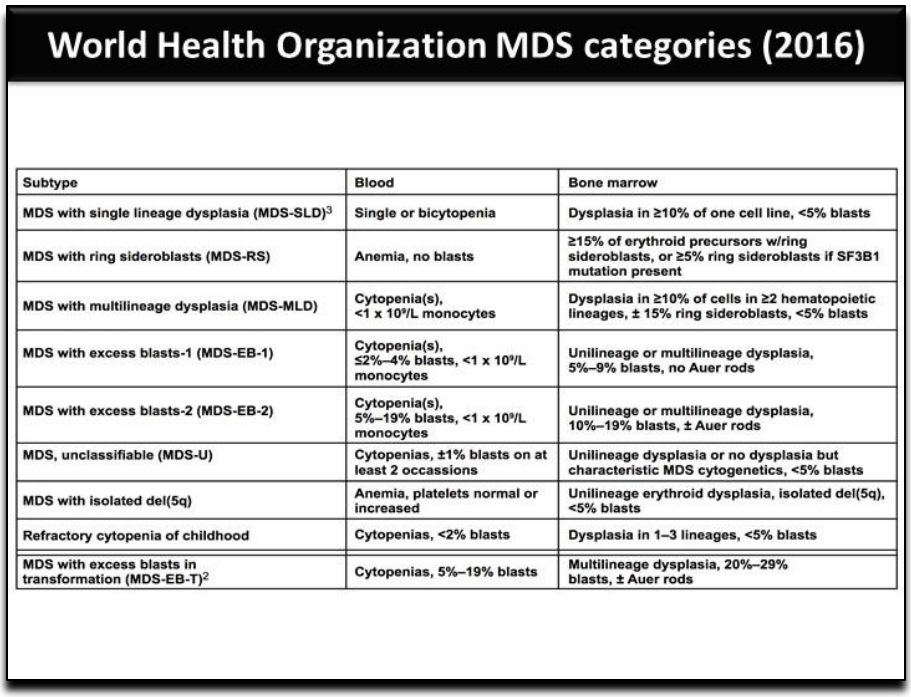


Chromosomes and Mutation Testing

When we look at the cells, we look at the shape of the cells themselves. And then we also take a deeper dive and look at the chromosomes that reside in the nucleus. This is where the genetic material is stored. And finally, many centers now are beginning to include gene sequencing, where they not only look at the structure of the chromosomes, they actually read out the individual basis that make up the DNA to find out if there are any errors or mutations present. And I'll show you how that can affect how we perceive the disease when we identify mutations that are particularly important.

Classification of MDS Subtypes

Now, once I've established the diagnosis of MDS in my clinic, the next thing I need to do is figure out, "What kind of MDS is this?"

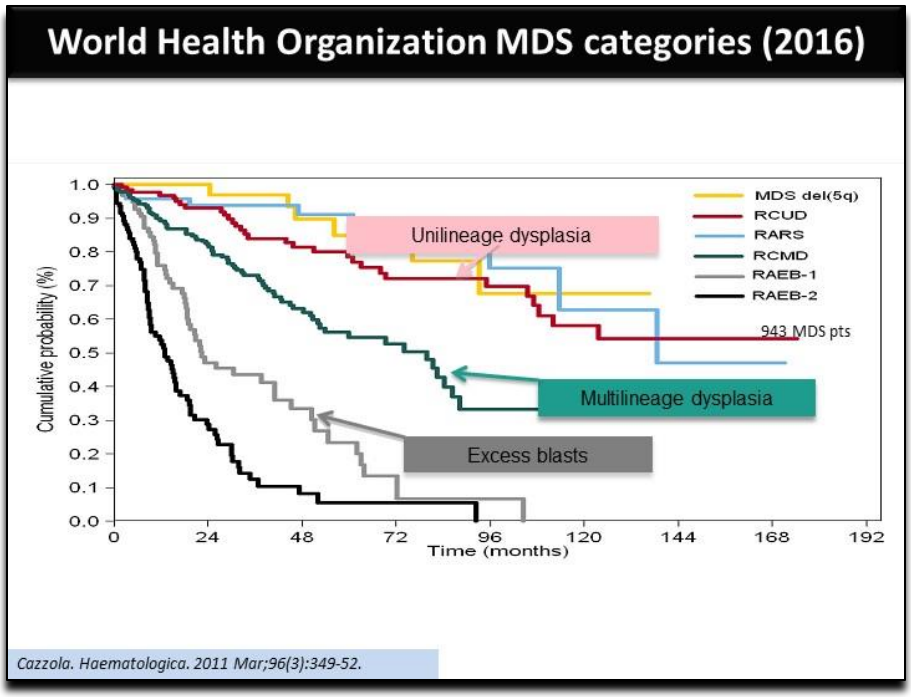


World Health Organization MDS categories (2016)

Subtype	Blood	Bone marrow
MDS with single lineage dysplasia (MDS-SLD)[3]	Single or bicytopenia	Dysplasia in ≥10% of one cell line, <5% blasts
MDS with ring sideroblasts (MDS-RS)	Anemia, no blasts	≥15% of erythroid precursors w/ring sideroblasts, or ≥5% ring sideroblasts if SF3B1 mutation present
MDS with multilineage dysplasia (MDS-MLD)	Cytopenia(s), <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in ≥2 hematopoietic lineages, ± 15% ring sideroblasts, <5% blasts
MDS with excess blasts-1 (MDS-EB-1)	Cytopenia(s), ≤2%–4% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 5%–9% blasts, no Auer rods
MDS with excess blasts-2 (MDS-EB-2)	Cytopenia(s), 5%–19% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 10%–19% blasts, ± Auer rods
MDS, unclassifiable (MDS-U)	Cytopenias, ±1% blasts on at least 2 occassions	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, <5% blasts
MDS with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del(5q), <5% blasts
Refractory cytopenia of childhood	Cytopenias, <2% blasts	Dysplasia in 1–3 lineages, <5% blasts
MDS with excess blasts in transformation (MDS-EB-T)[2]	Cytopenias, 5%–19% blasts	Multilineage dysplasia, 20%–29% blasts, ± Auer rods

World Health Organization MDS Categories (2016)

And we have a handy guideline that is produced by the World Health Organization (WHO). It puts MDS into a variety of several bins that are shown here. No need to really remember this, but just understand that they tell us something about the nature of the disease.



World Health Organization MDS Categories (2016)

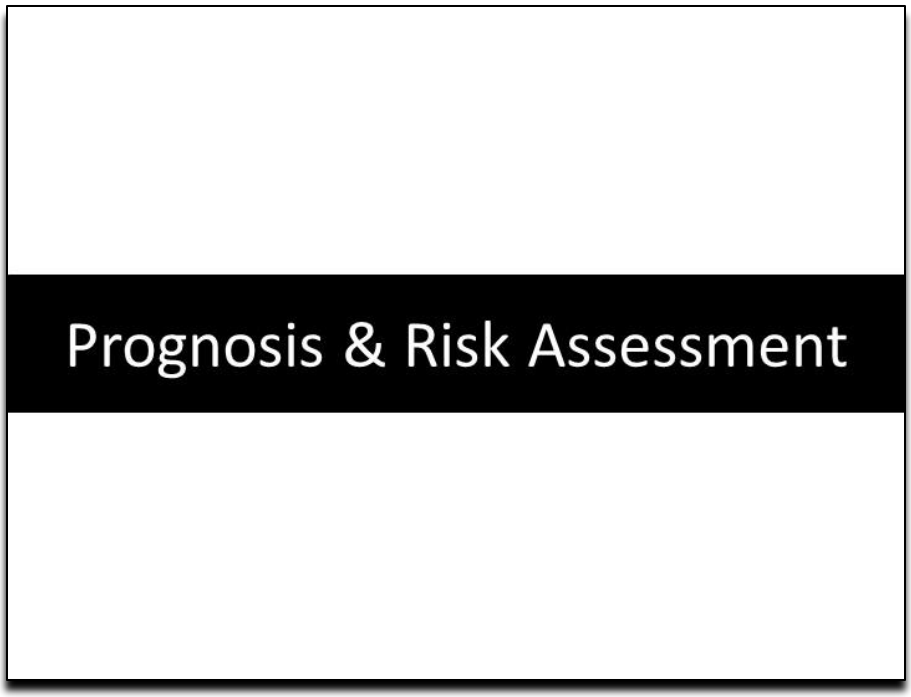
There are some patients that, for example, only have one type of blood cell affected, or they have single lineage dysplasia. There are some patients that have a particular finding called ring sideroblasts, and this has important prognostic implications. And then there are patients that have some of those immature cells that are leukemia-like cells in the bone marrow that we call blasts. And they are put in this category of patients that have MDS with excess blasts.

There is one category that I'll have you pay special attention to. These are patients that have MDS with a deletion of 5q. What that's referring to is patients who have a loss of part of chromosome 5. These patients are important to recognize because we have a therapy that's particularly effective in this population. And I'll talk more about that later.

Now, one of the reasons that putting patients into these different classifications is helpful is because they have very different outcomes. Some patients that have lower risk disease will tend to have only one lineage affected or will have few of these leukemia-like cells, whereas other patients who have higher risk disease are more likely to have excess blasts or an increasing number of leukemia-like cells in the bone marrow.

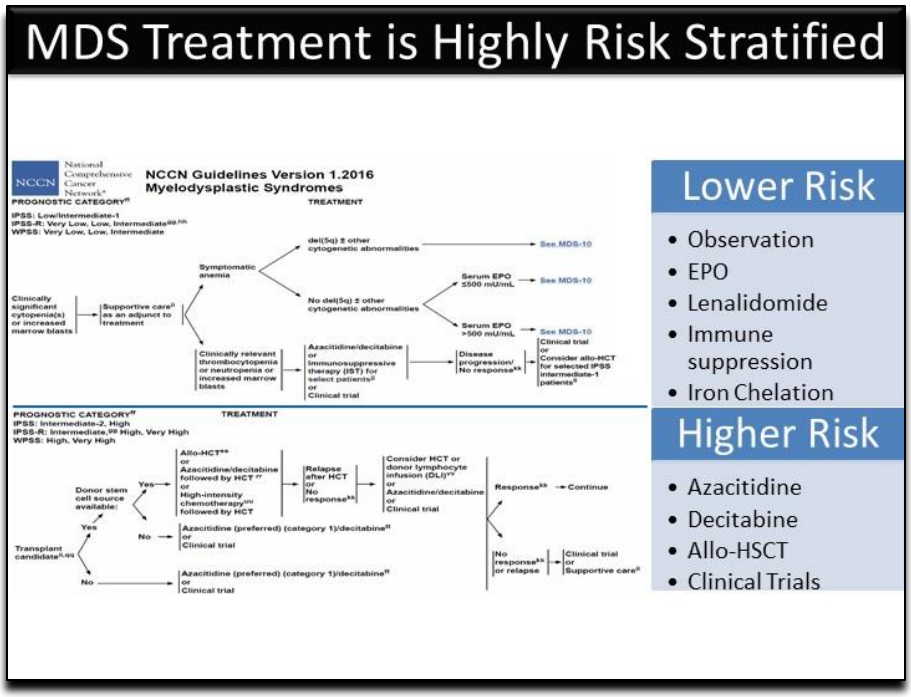
So, this is a survival curve that shows how long people generally live—or a population might generally live—after their diagnosis. And you can see that patients that have unilineage dysplasia—or only one abnormality in their bone marrow—tend to survive longer than patients that have multiple cell lines affected or patients that have these leukemia-like cells in their bone marrow.

Now, I'll point out that these data that I'm showing you here reflect survival in the absence of treatment. And what we hope is that treatment can modify these survival curves and improve outcomes in this disorder.



Prognosis & Risk Assessment

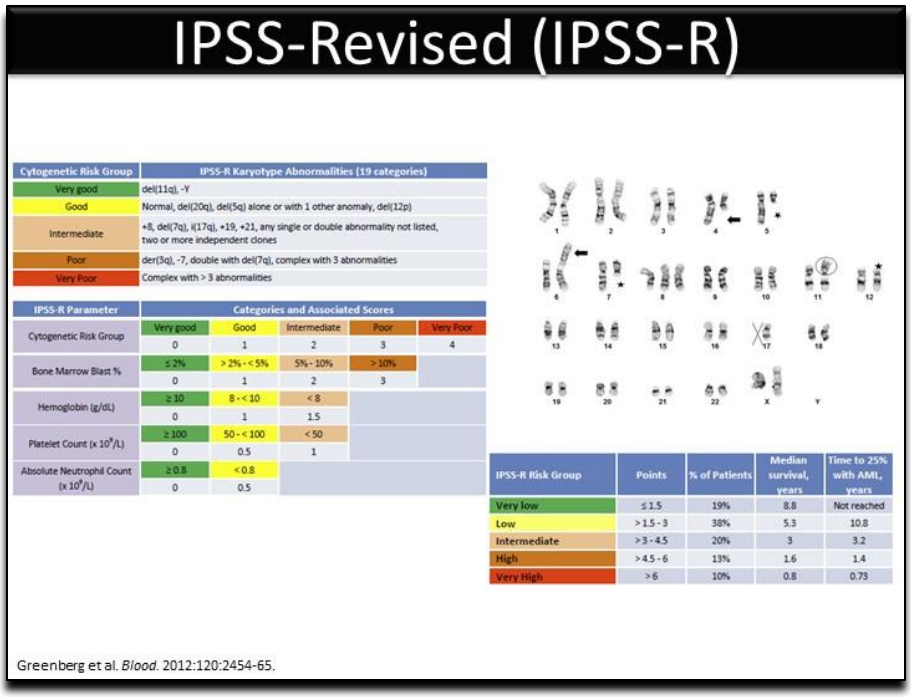
So next, I'd like to talk about what I do in the clinic. I've diagnosed the patient with MDS. I've determined what type of MDS they have. The next most important step is to really hone in on what their prognosis is or what their outcome is likely to be in the absence of treatment. This is going to help me decide if I have an aggressive MDS that I need to treat immediately or if I have a more slowly progressive process that may not even have any symptoms at the moment that I could simply observe.



MDS Treatment is Highly Risk Stratified

We have some guidelines that help us make these decisions—these are from the NCCN, or the National Comprehensive Cancer Network—that help us understand how we should approach patients who have a diagnosis of MDS. They divide their recommendations into two major projects: one that's for lower risk patients and another that's for patients with higher risk disease.

And I'll tell you in a moment how we determine that risk. But what you'll notice is that the recommendations for treatment options in those two categories are very different, so it's very important to identify the risk in a patient with MDS correctly because it's really going to change the options that we present to them.



IPSS-Revised (IPSS-R)

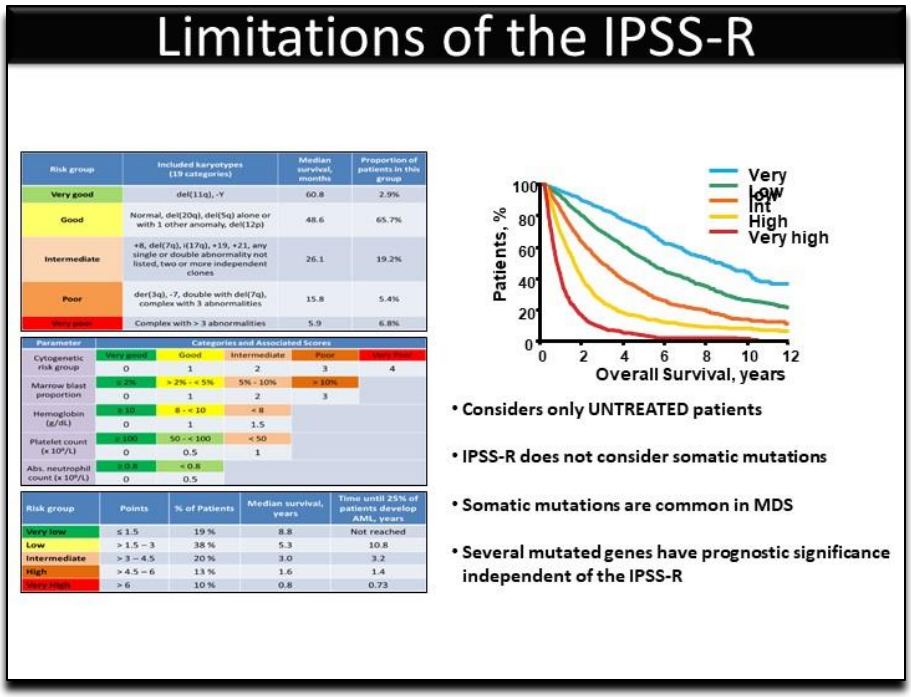
So, how do we actually determine risk in MDS in practice? We have several tools that can help us. I think the one that I would consider the current gold standard is the IPSS, or the International Prognostic Scoring System, that was revised a few years ago. Now, this considers several features of the disease.

It looks at the chromosomes, which I'm showing you in the upper right-hand corner there, and any chromosomal abnormalities that might be present; it considers how many blasts or leukemia-like cells are in the bone marrow; and it considers how low the blood counts are. Patients with more severe anemia or more severe low platelet counts will get a higher score on this scale.

And after you add up all the points in those categories, you can put patients in one of five risk groups, ranging from very low all the way up to very high, with about two-thirds of the patients being in very low, low, or intermediate risk groups.

If we look at outcomes of patients in these different risk groups that's shown here on the right, we can see that patients with very low risk have a very long predicted survival. In fact, it's not dramatically different than the predicted survival for patients who are in their 70s and 80s, which accounts for the majority of patients with MDS.

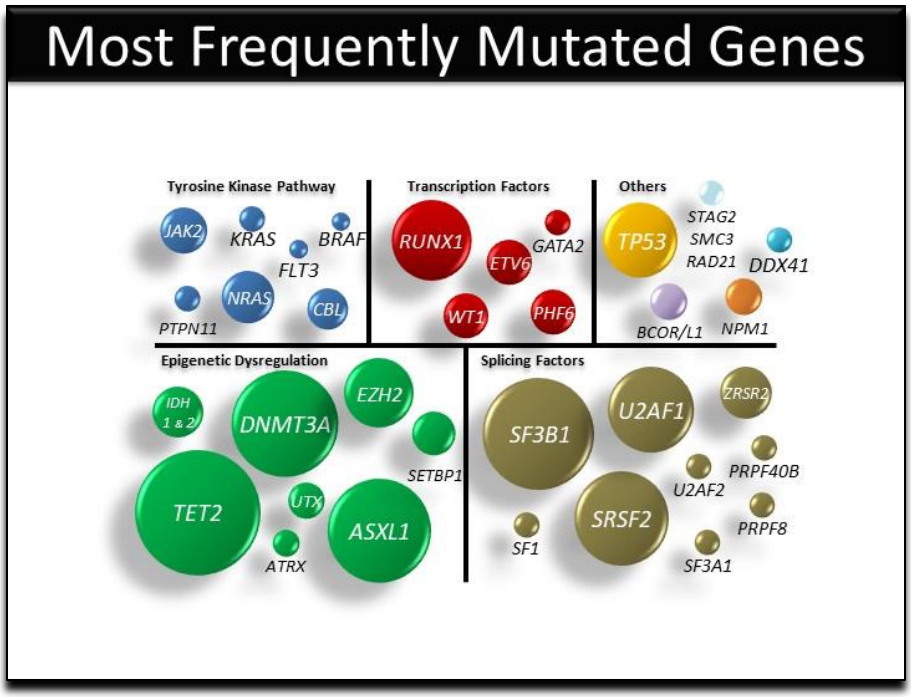
However, patients with very high-risk disease are much more likely to suffer a consequence of their disease than they are to die of something else. So, it becomes very important to understand risk in order to determine how we treat patients. I will remind you that these curves talk about untreated patients. And what we hope is that with current and emerging therapies we can improve outcomes all around.



Limitations of the IPSS-R

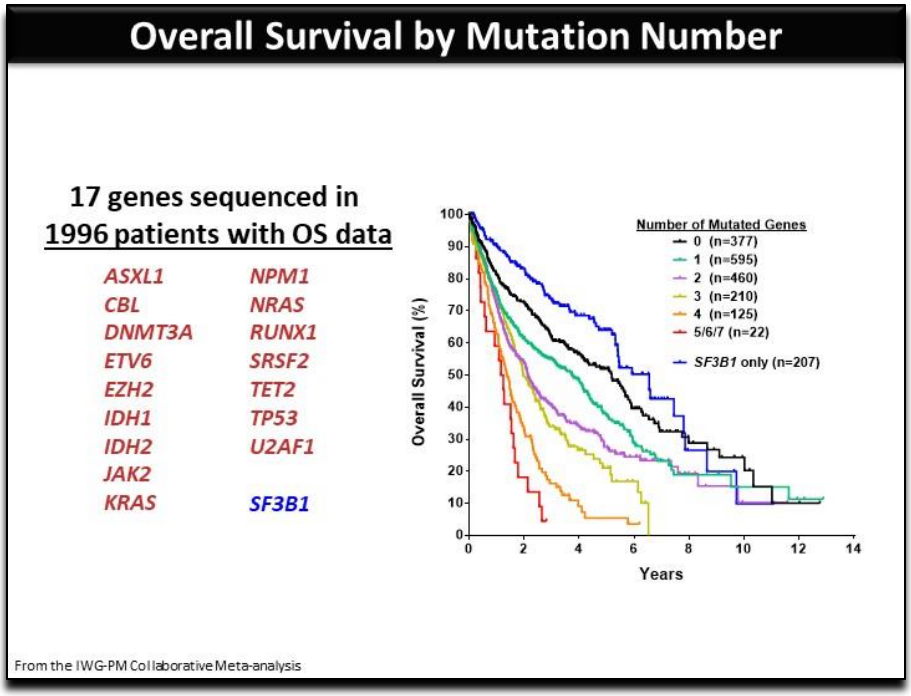
Now, the one thing that you don't see included in the IPSS-R is any consideration of mutations that were detected by DNA sequencing. And as I mentioned before, many centers are starting to do this routinely now. So, what we're working on as an MDS community is how to incorporate mutation information into this assessment of risk that is so important to determining how we treat patients with MDS.

And I'll show you some examples of that. When I started in this field about 15 years ago, we didn't really have a great understanding about what the genetic drivers of MDS might be. We knew that there were a couple of genes that could be mutated in this disease. But over the last 10 or 15 years, we've learned that there are many, many genes that can actually occur.



Most Frequently Mutated Genes

I show some of the gene names here. And it's not important to know any one of them, but you can see that several of them are fairly common, based on the size of the circles that represent them. And in fact, we can identify mutations in about 85% to 90% of patients with MDS.



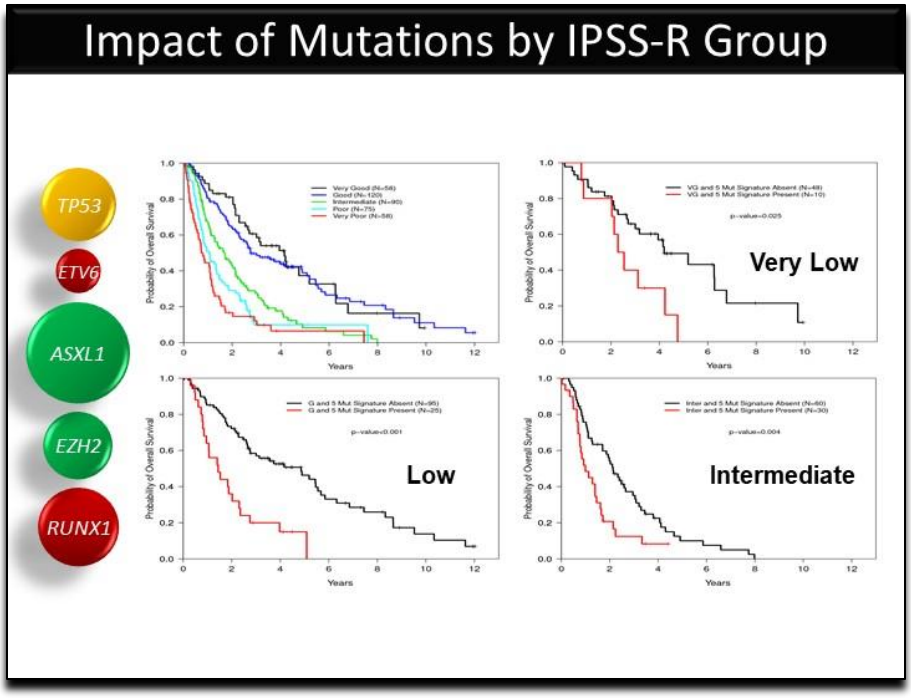
Overall Survival by Mutation Number

One of the things that we've learned is that the more mutations that a person has, the more likely it is that they have higher risk disease or more aggressive disease. The one exception to this is mutations

in a gene called *SF3B1*. Mutations in this gene seem to identify patients with MDS who have very different outcomes, and I'll show you that here in the survival curve.

Patients with only an *SF3B1* mutation, shown here in the blue, tend to live longer than patients who have none of these mutations that I show here on the left or that have one or more of those mutations.

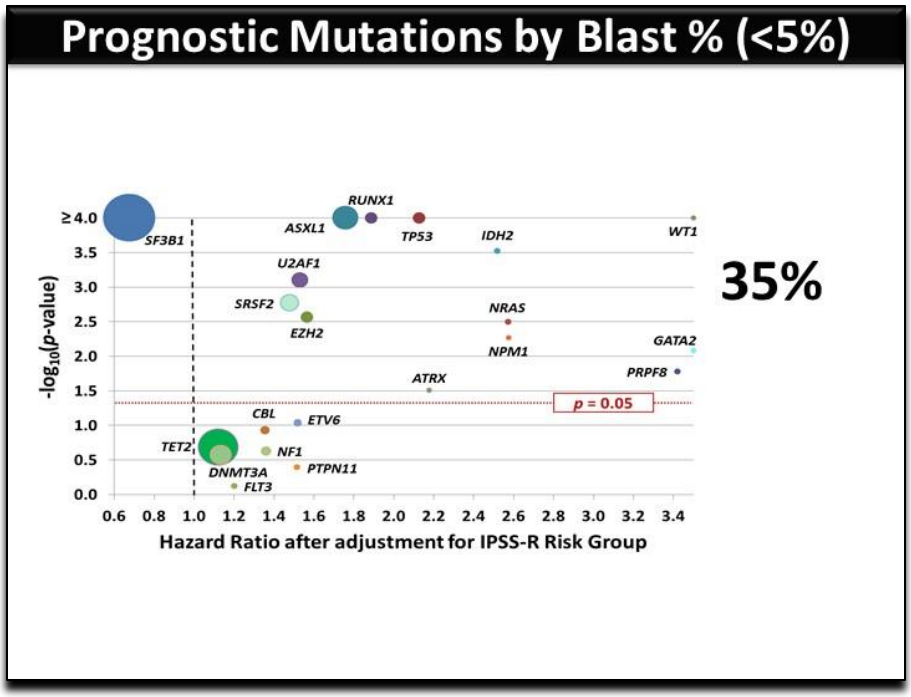
However, patients that have four, five, six, or even seven mutations identified on DNA sequencing tend to have more aggressive disease that would need to be treated with more aggressive therapies.



Impact of Mutations by IPSS-R Group

Just to show you an example of how mutations can add information, if we take patients that we thought had very low risk disease according to the IPSS-R and we identify those that have mutations in one of these five genes on the left here, their survival, shown in the red line, moves to the left—meaning that their predicted survival is actually shorter than we would have thought based on the IPSS-R alone.

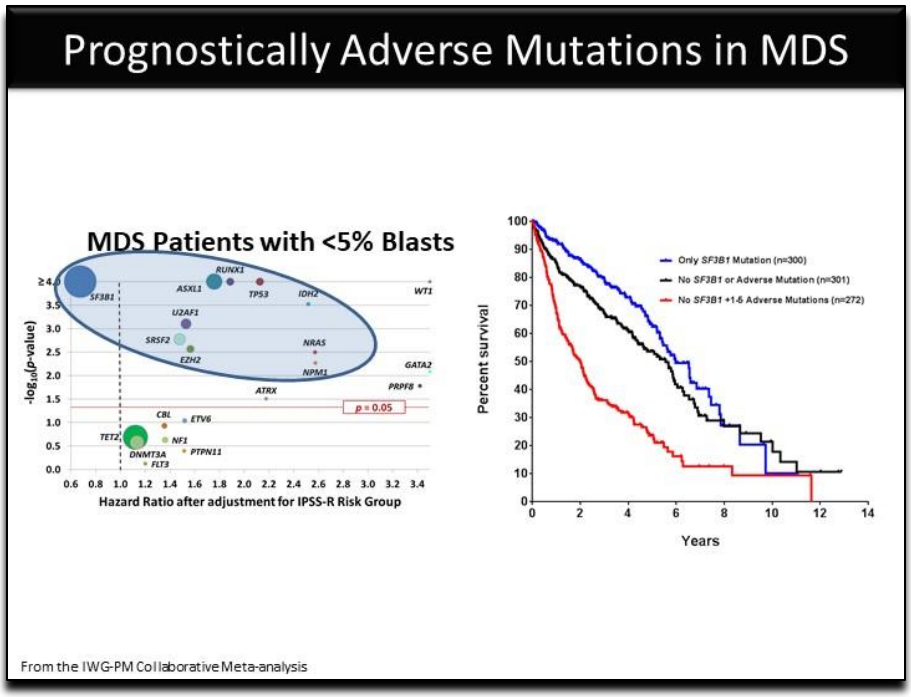
The same is true for patients who start in the low risk group. If they have a mutation—and about a third of them do—then their survival is not as good as we might have predicted. And even in the intermediate risk group, who are just on the edge between what we consider low and high risk, if having a mutation which occurs in about 40% of patients—having a mutation is associated with more aggressive disease that we should treat more aggressively than we probably do in the absence of that information.



Prognostic Mutations by Blast % (<5%)

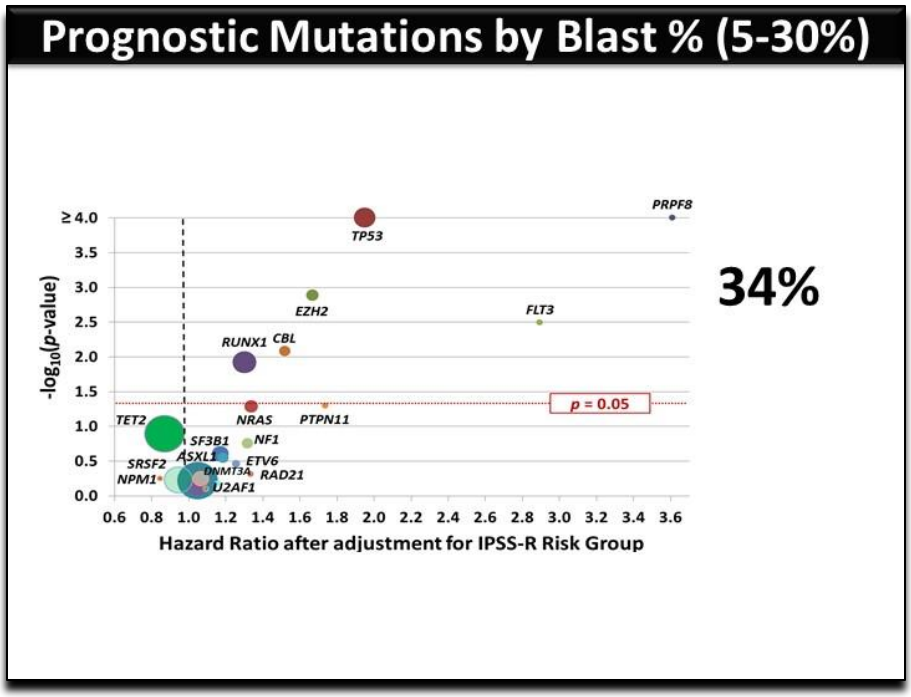
I'm going to show you these data in a slightly different way. This is data that was generated by studying thousands of patients from centers all around the world who were sequenced at those centers and then put together in a massive meta-analysis.

What we find is that there are many genes that are to the right of that dotted line that are associated with increased risk, even after we take into account the IPSS-R. Everything that is above the red line on the Y-axis is considered significant. And you can see that there are multiple different mutated genes that occur in that quadrant. And about 35% of patients will have one or more mutations in these genes.



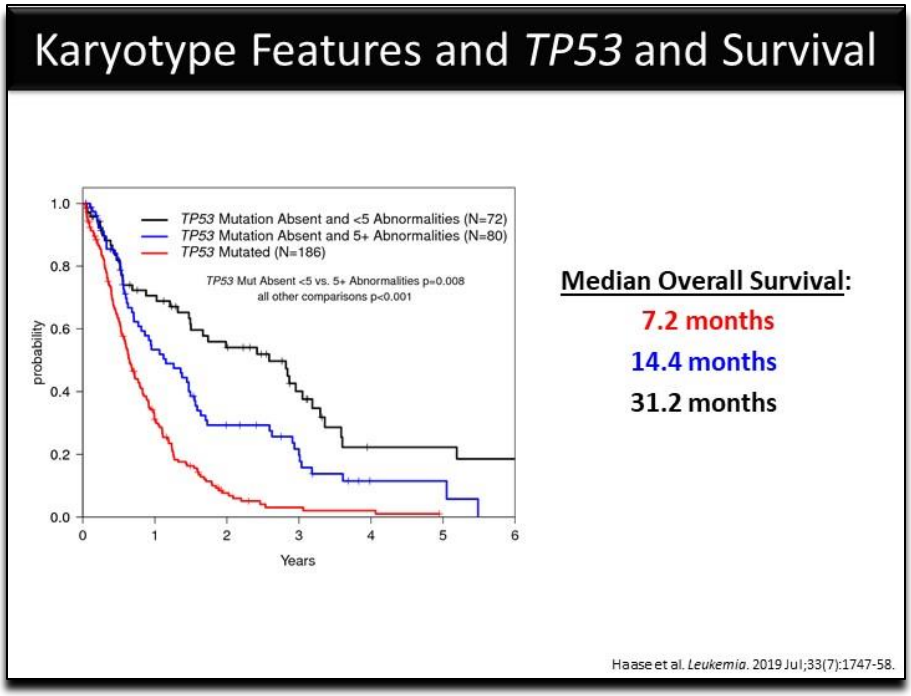
Prognostically Adverse Mutations in MDS

Just to show you what that can mean: If we take those patients that have mutations in one of those genes shown in this blue circle here—these are the most common mutations that we identify—then the survival goes from being on the black line to being on the red line. So, the predicted survival is less than half of what we would have thought once we understand that these mutations are present.



Prognostic Mutations by Blast % (5-30%)

Now again, patients who have *SF3B1* mutations on the other hand actually do a little bit better, suggesting that their type of MDS is more slowly progressive or less likely to cause life-threatening consequences.



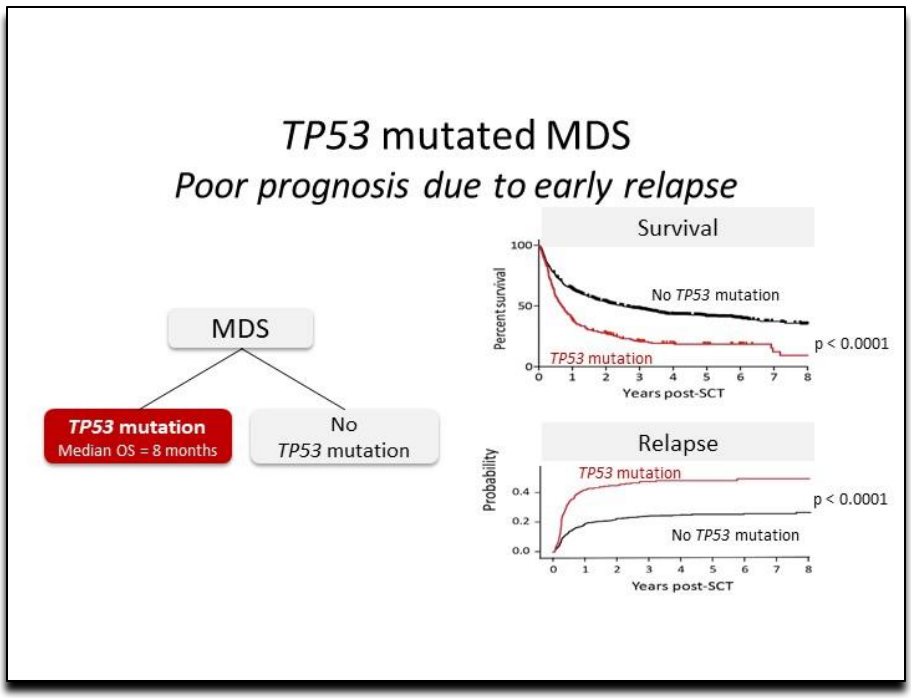
Karyotype Features and TP53 and Survival

I will point out that even in patients who have high risk disease by the IPSS-R, there are mutations that gives us additional information. And I want you to focus on one particular mutation. This is a gene

called *TP53*. This is a mutation that occurs in about 10% to 12% of patients with MDS and unfortunately is associated with a very poor prognosis.

It is associated with multiple chromosomal abnormalities, low blood counts, and a high rate of progression to acute leukemia. However, there are some patients that looked like they had very high risk disease, and when we sequence them we don't find a *TP53* mutation. And those patients actually do better than we might predict.

So, we've begun to recommend that patients who have MDS have gene testing done to see if they have a mutation in this gene, particularly if they plan to go onto more aggressive therapies, like bone marrow transplant. Because you can see that the survival difference in patients who have a *TP53* mutation, shown here at 7.2 months on average, is much lower than the survival of patients that have normal chromosomes and have no *TP53* mutation, which is shown here at about 31 months.

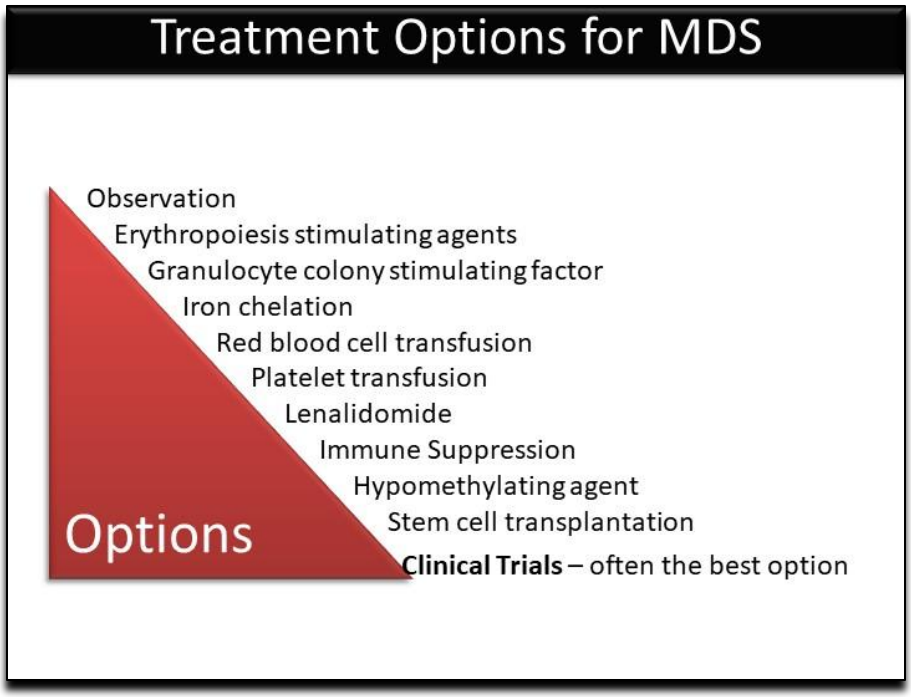


***TP53*-Mutated MDS**

What we would have hoped is that treatment might change these outcomes. And unfortunately, that doesn't seem to be the case. Patients that are treated with a bone marrow transplant, for example, and have a *TP53* mutation are much more likely to have their disease come back after the transplant and are much less likely to survive 5 years or more. So, we need better therapies for patients with *TP53*. And near the end of the call today I'll give you some examples of where we're making some progress on that front.

Risk-Adapted Patient-Specific Therapy

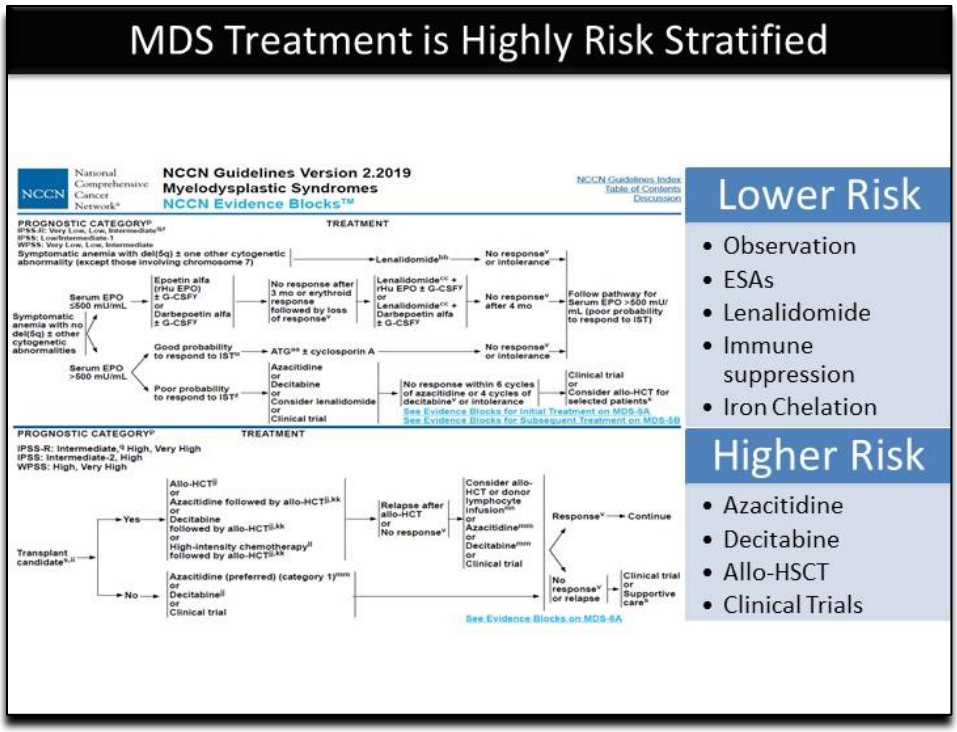
So, now that I've gone through and identified a patient as having MDS, classified their disease, and assessed their risk, I can start to make decisions about how to treat them. So, we call this risk-adapted, patient-specific therapy—or a form of personalized therapy—because we're taking all the information about the patient in front of us and using it to help come up with a treatment plan.



Treatment Options for MDS

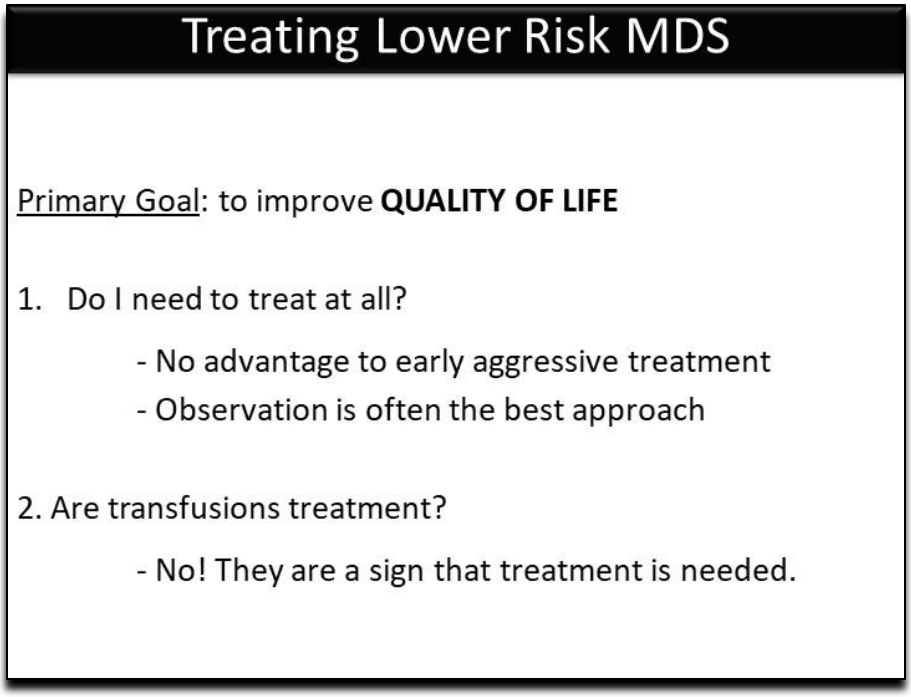
And we have a variety of different treatment options, some of which are shown here. And I'll go into greater detail. I do want to point out that all of these treatment options leave something to be desired.

And a clinical trial of a new agent is often a best option for patients. And if that is available for you at your doctor's site or available for you in your area, that's something I would strongly encourage you to consider.



MDS Treatment is Highly Risk Stratified

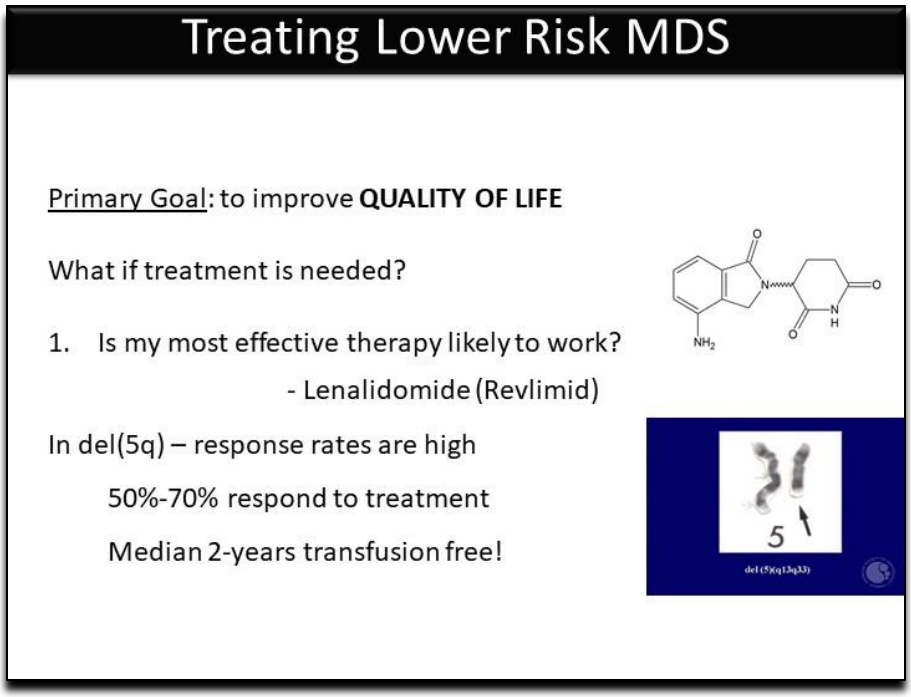
So as I mentioned, the treatment of MDS is highly risk stratified—that we really need to divide patients into higher risk and lower risk—because those different treatment options are going to be very different for those individuals.



Treating Lower Risk MDS

So, if I have a lower risk MDS patient that I need to decide about treatment, the first thing I ask is whether or not I need to treat at all. If a patient has very few symptoms—and some patients have no symptoms at all, they only have abnormal blood counts—it's very unlikely that I'm going to make them feel any better. I can certainly make them feel worse. And I don't want to do that if all we're doing is trying to make a number better without really improving their quality of life.

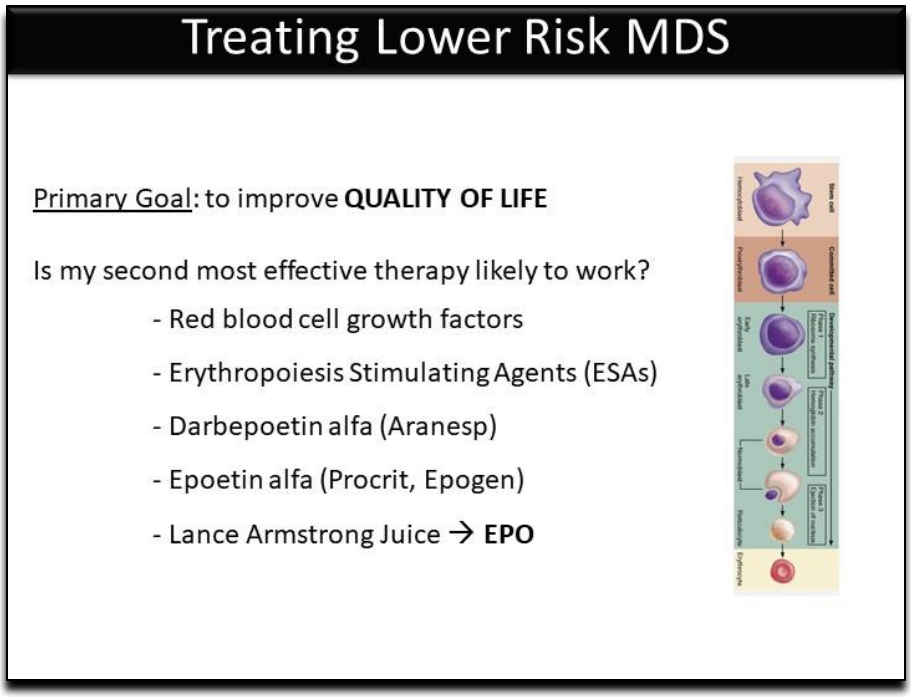
The one question that I often get is, "Are transfusions of blood cells considered treatment for this disease?" And I would say that they are not. They are supportive care, which is important, but they are a sign that the disease is advanced enough that we now need to consider some sort of therapy. So, having a requirement for transfusions is an indicator that a patient should be treated.



Treating Lower Risk MDS

So, if I do have a patient that I think needs treatment because they are having symptoms or requiring transfusions, then the first question I ask myself is, "What is my most effective drug?" And at the moment, in lower risk MDS our most effective therapy is a drug called lenalidomide (Revlimid®). Now, lenalidomide (Revlimid®) is particularly effective in a small subset of patients.

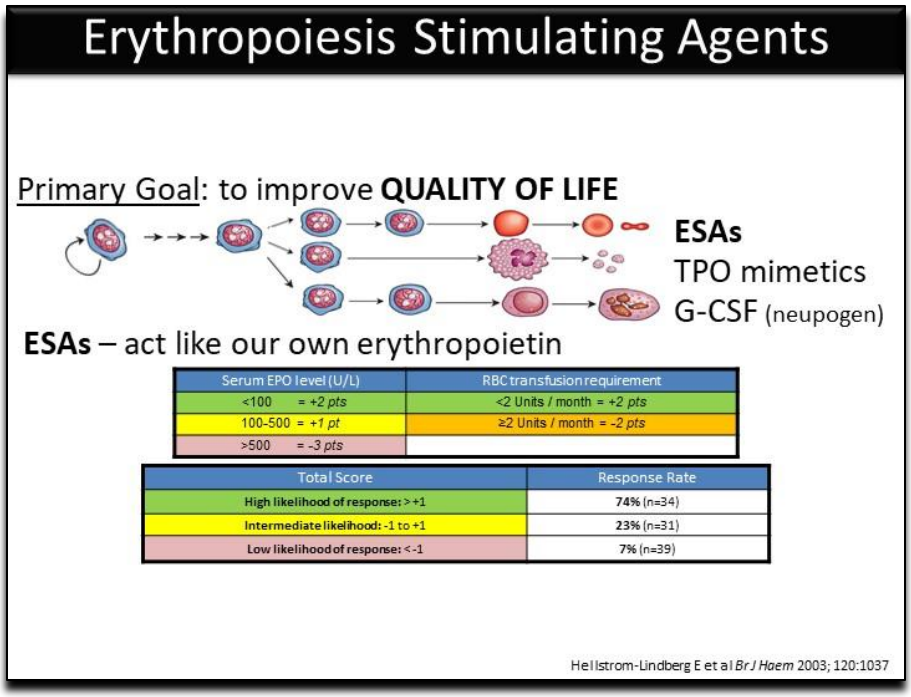
Unfortunately, it doesn't work beautifully for everyone. But, the patients that are likely to receive the greatest benefit from this drug are those patients that I mentioned earlier that have a deletion of chromosome 5. If part of chromosome 5 is missing, their disease is particularly vulnerable to this medication. Patients with this condition have a very high response rate, their hemoglobin tends to rise quite dramatically, and [they] are often transfusion-free for quite a long time. So, if this is an option—which it is for about 5% to 10% of lower risk MDS patients—then this is the drug that I would reach for first.



Treating Lower Risk MDS

Now, if a patient does not have a deletion of chromosome 5q, then lenalidomide (Revlimid®) may not be the best drug for them and I'll consider my second most effective therapy. And these are red blood cell growth factors. These are particularly effective at treating patients who have anemia and not so effective at treating other kinds of low blood counts, like low neutrophil or low platelet counts.

Now, there's a variety of red blood cell factors that are out there. You maybe have heard of them referred to as ESAs or by their specific names, like darbepoetin (Aranesp®) or epoetin (Procrit®, Epogen®). Some people might recognize that these are drugs that certain athletes have abused in order to increase their hemoglobin in the past. And they mimic a normal hormone that our own body makes, called erythropoietin, or epo.

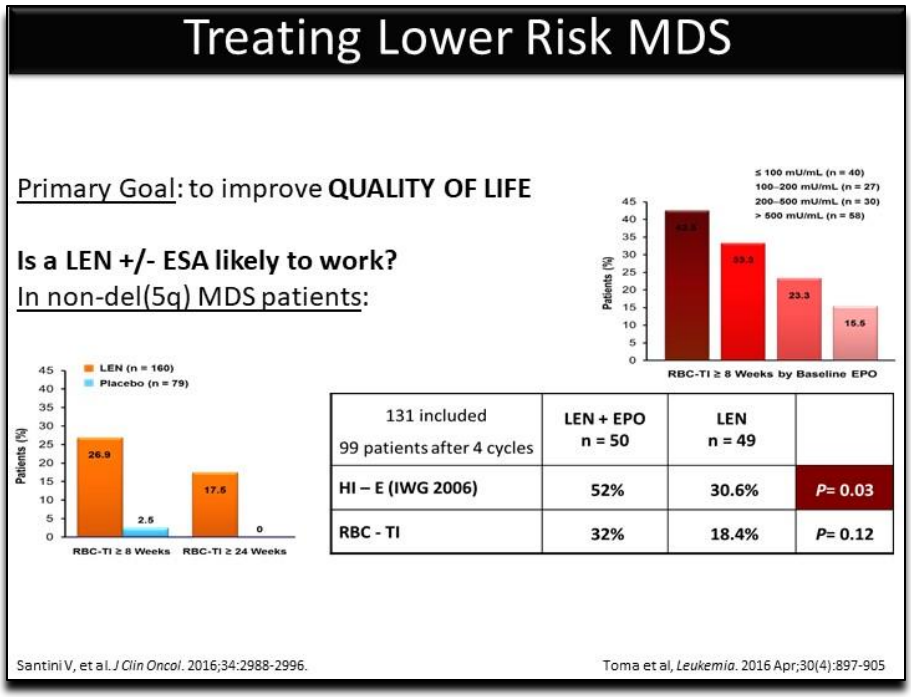


Erythropoiesis-Stimulating Agents

So, how do we determine if a patient is a good candidate for one of these erythropoiesis-stimulating agents or epo-like drugs? Well, one thing that helps is that we can measure a person's own production of this hormone epo. If they don't make very much epo, then it's possible that my giving that patient more epo in the form of these medications might help improve their red blood cell production.

However, if the patient is making a large amount of epo on their own and still not increasing their hemoglobin, it's unlikely that my giving them more is going to be helpful. Also, these drugs don't increase the red blood cell production very dramatically. So, if a person is requiring a lot of blood transfusions, it's very unlikely that these medications, even if they help somewhat, are going to be able to prevent the need for ongoing blood transfusions.

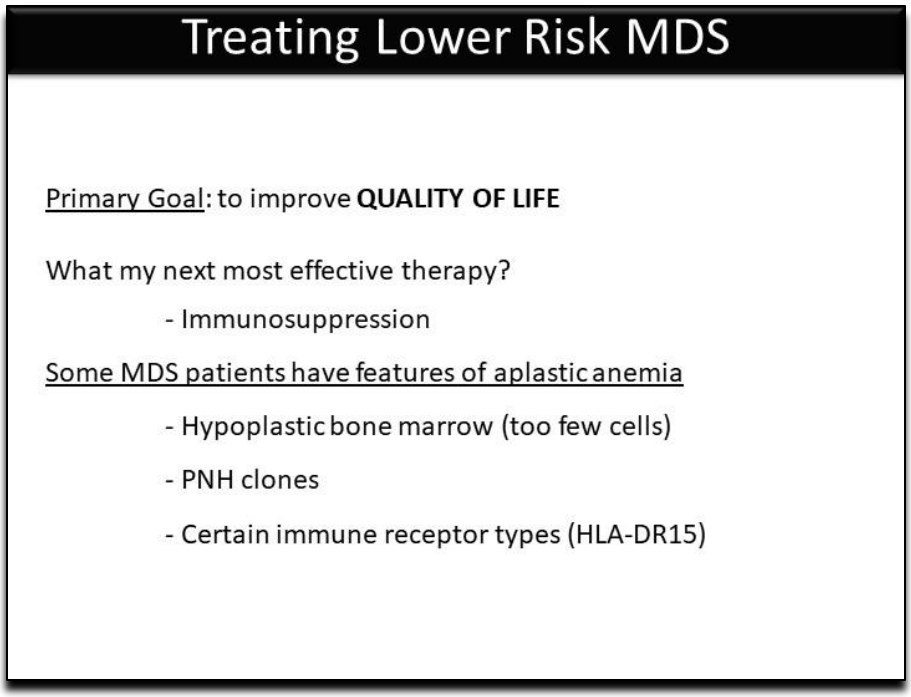
So, we take those things into consideration. A person who has a low transfusion burden and a relatively low epo level has a very high likelihood of responding to these medications—about 75%—whereas a person who already makes a lot of epo on their own or requires a lot of transfusions is very unlikely to respond.



Treating Lower Risk MDS

Now, recently we have more information about using lenalidomide (Revlimid®) in combination with the erythropoiesis-stimulating agents. And this is a result of a study that was published a couple of years ago that showed that even in patients who don't have this deletion of chromosome 5q, if you treat them with lenalidomide (Revlimid®) and combine it with an erythropoiesis-stimulating agent, you can see response rates that are on the order of about 27% to 40%, which is not bad. Unfortunately, these responses are not very durable. They last for a few months, but they don't necessarily last years or decades. So, we still do need better therapies even in this area.

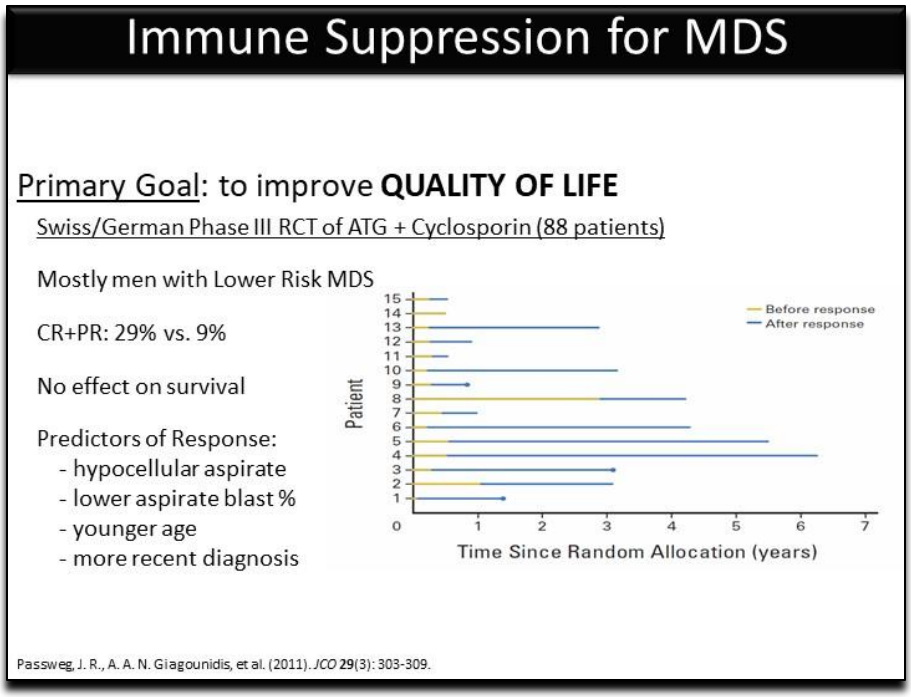
But, just to show you an example: In the study where they combined lenalidomide (Revlimid®) and erythropoietin, the hematologic improvement rate was over 50%. Whereas when they used lenalidomide (Revlimid®) alone, it was about 30%. So, we will often combine these two medications in patients that we think are good candidates. And just as we talked about before, the lower the epo level the greater the response rate.



Treating Lower Risk MDS

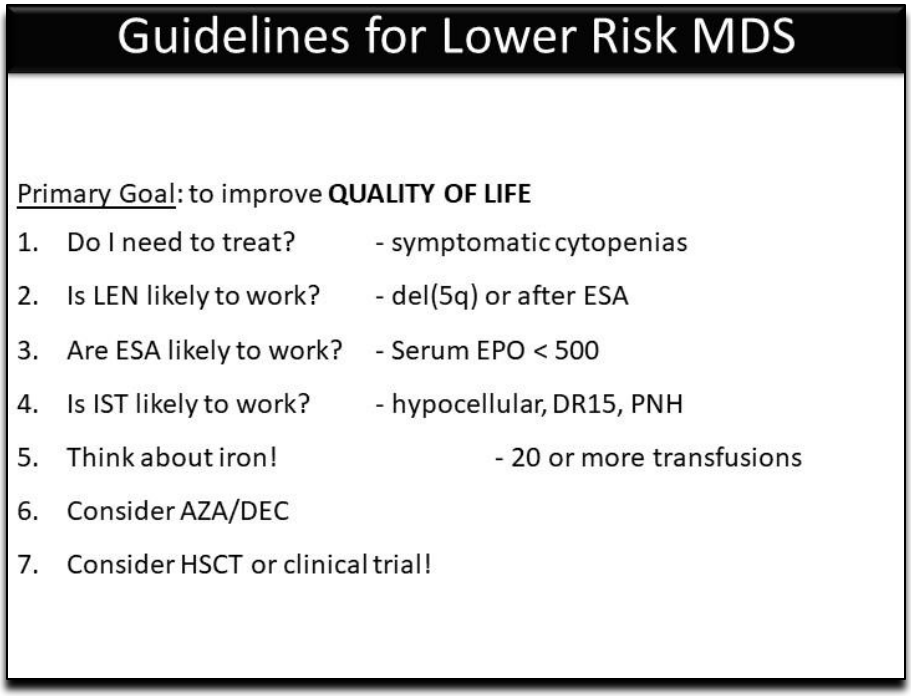
So, if we've tried that, or we think that that's not a good option for patients, we do have another option for lower risk MDS patients. This is immunosuppression. Often, we think the immune system is recognizing the abnormal bone marrow and attacking it in a way that causes damage and prevents normal blood cells from developing. So, we can use very immunosuppressive therapies that we normally use in patients who have aplastic anemia.

And these features often that help us determine if a patient is a good candidate include having bone marrows that kind of look like aplastic anemia, where they have very few cells instead of too many—evidence of immune destruction in the form of little clones that have emerged in response to the immune pressure.



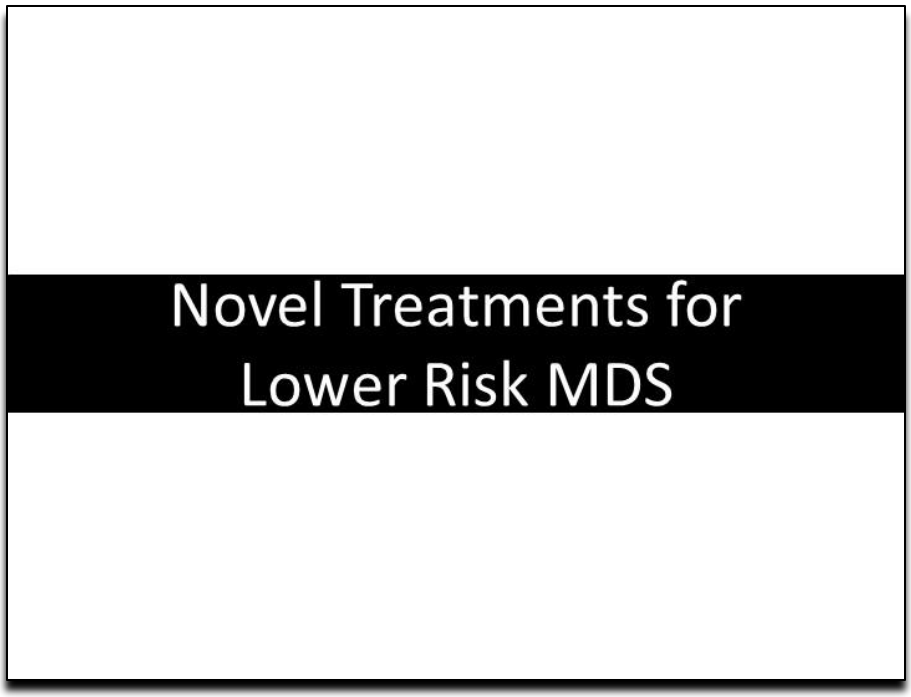
Immune Suppression for MDS

And the response rates are about 29% or so. Interestingly, some of these responses are quite long-lived. They also don't occur overnight. Patients can often take months before they actually get a response. But if they respond, they can respond for quite a long time.



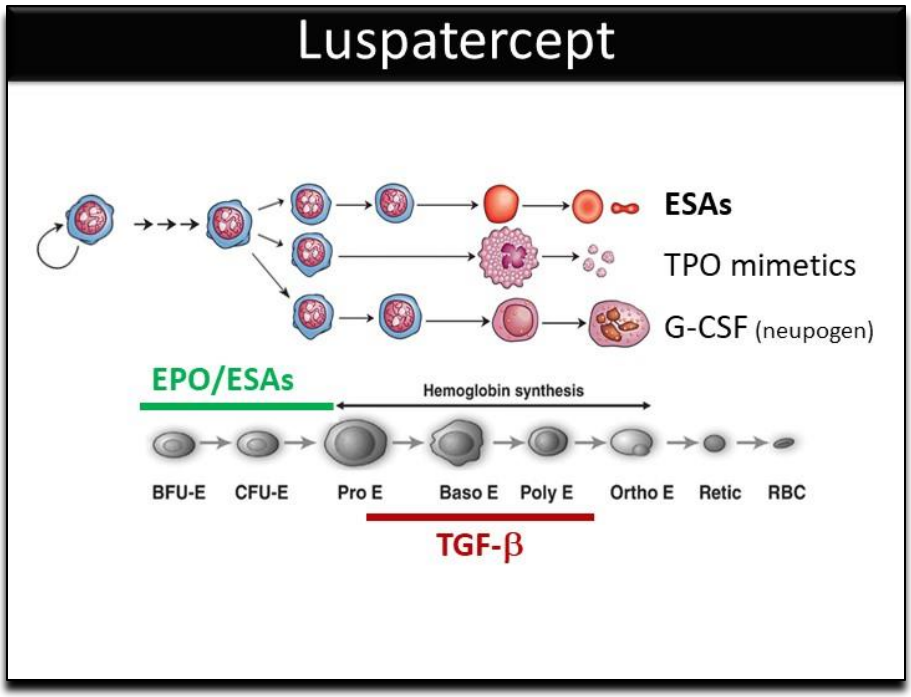
Guidelines for Lower Risk MDS

So, to summarize how I think about lower risk MDS today, I think about whether I need to treat at all and then whether some of my more effective options are going to be useful in the patient I have in front of me.



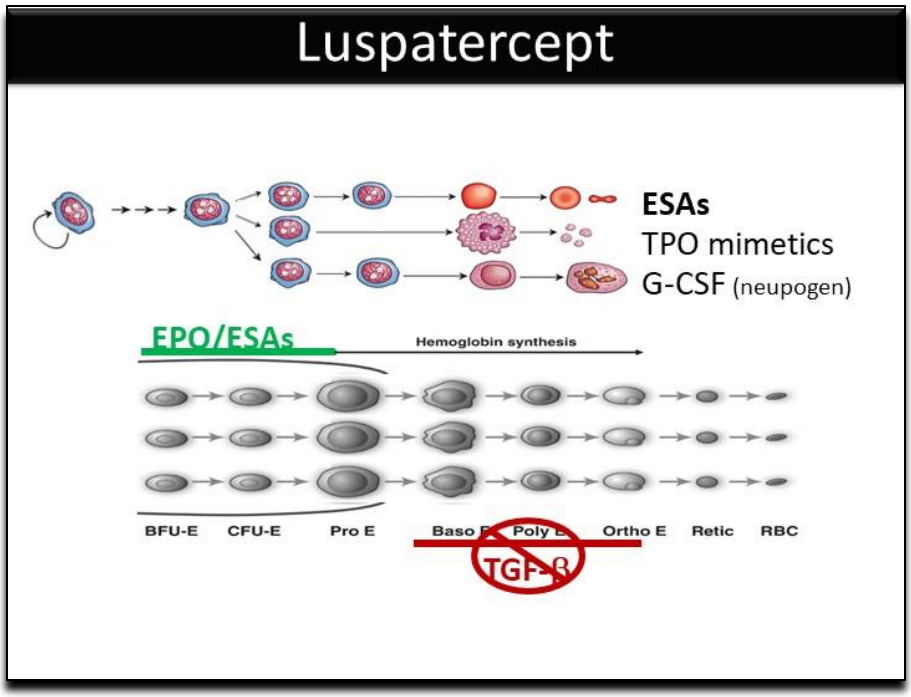
Novel Treatments for Lower Risk MDS

But we have finally the prospect of novel therapies to help us treat patients with lower risk MDS.



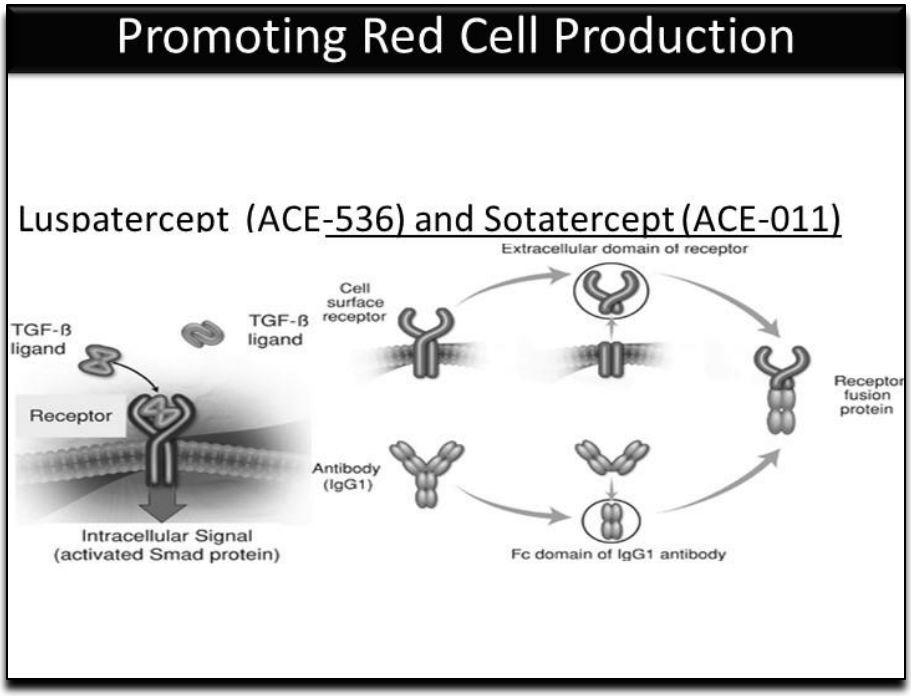
Luspatercept (Reblozyl®)

And one that I want to talk about is a drug that was recently approved for a different condition. This drug is called luspatercept (Reblozyl®). Now, luspatercept (Reblozyl®) works in the same pathway that erythropoietin does. It helps produce more red blood cells.



Luspatercept (Reblozyl®)

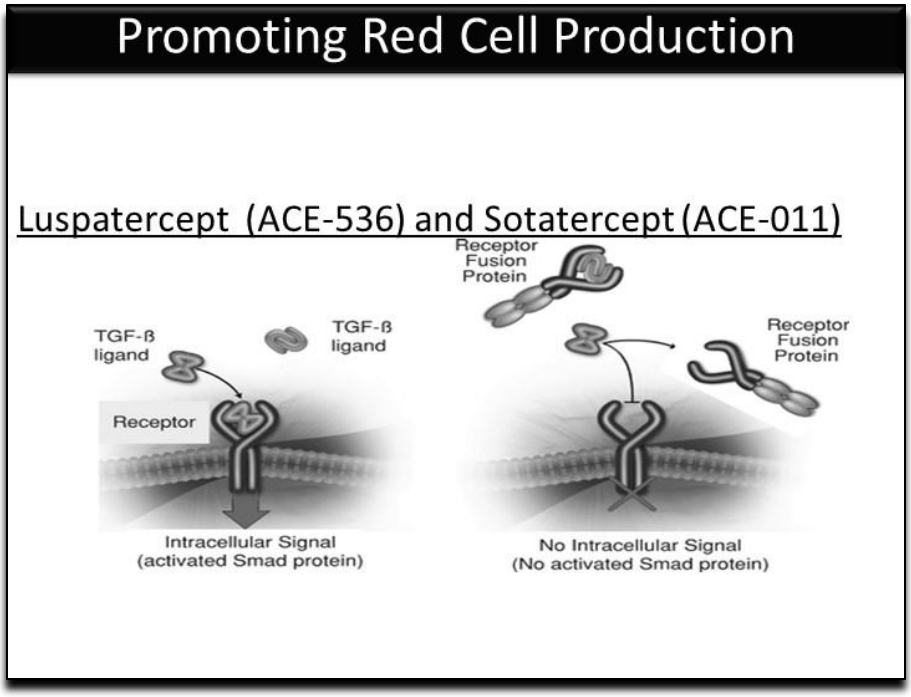
Now, unlike erythropoietin, which is like adding fuel to the fire, this drug luspatercept (Reblozyl®) is like taking the brake off of a car and allowing it go faster. Under normal circumstances, our red blood cell production is very tightly controlled. And we have both an accelerator and a brake that determines how many red blood cells we make.



Promoting Red Cell Production

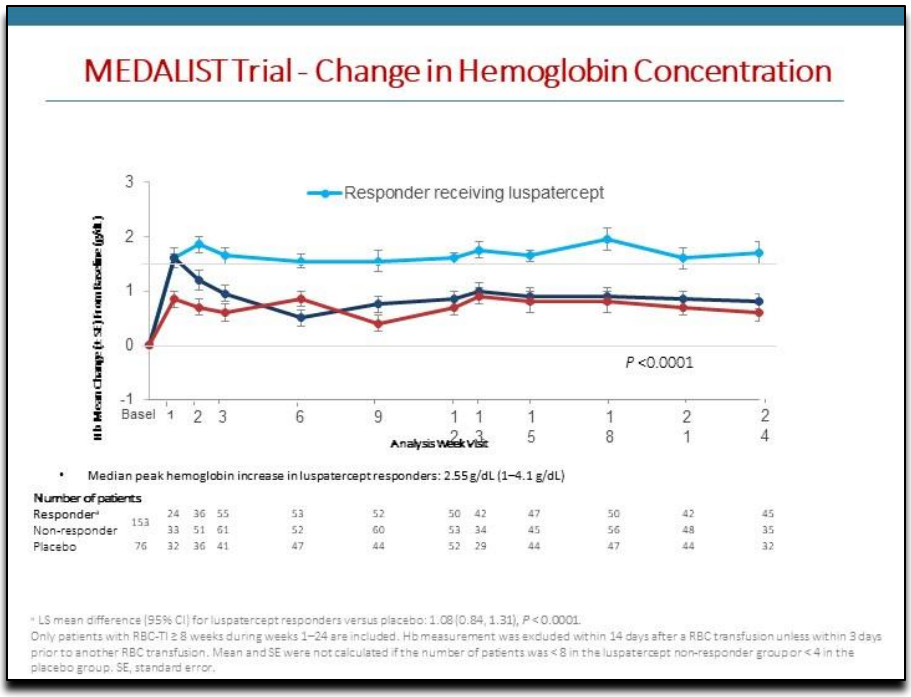
Now in MDS, if we increase the number of cells going into the pipeline we don't necessarily get more cells at the end unless we can affect this brake. And this brake is a class of proteins called tumor

growth factor suppressors beta, or TGF-betas. And if we can block these proteins, we might be able to get more red blood cells out.



Promoting Red Cell Production

So, the drug luspatercept (Reblozyl®) is actually a protein that is infused or given as an injection. And it looks like the normal receptor for TGF-beta. However, it floats around in the bloodstream. And when it finds TGF-beta, it binds it and prevents it from acting on cells normally. So, that brake is removed.

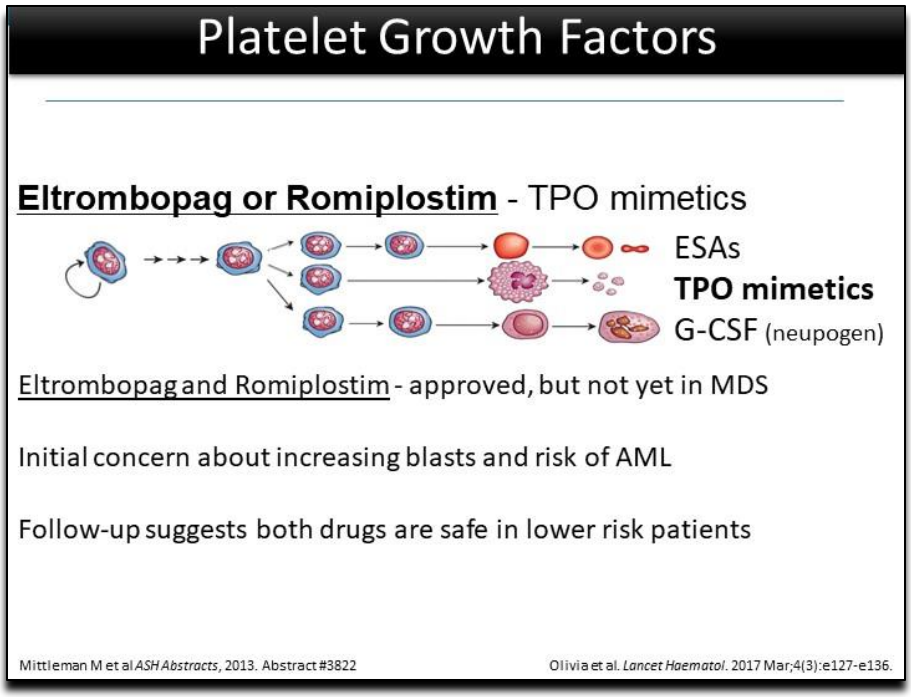


MEDALIST Trial – Change in Hemoglobin Concentration

In the clinical trial that was described at the American Society of Hematology meeting last year, we saw that patients had a very nice response to this drug. About 37% of patients showed improvements in their blood counts. And some of those improvements were quite substantial and quite long-lived, as shown here in the light blue line, where we see the increase in hemoglobin over time compared to patients who got placebo that were shown in red.

Now, this drug was expected to be reviewed by the FDA sometime in the middle of next year. However, during the meeting at ASH, we learned that it was likely to be accelerated. And we hope that the approval comes sooner than that. Although as I mentioned, it is already approved for another condition, and some physicians are considering prescribing it.

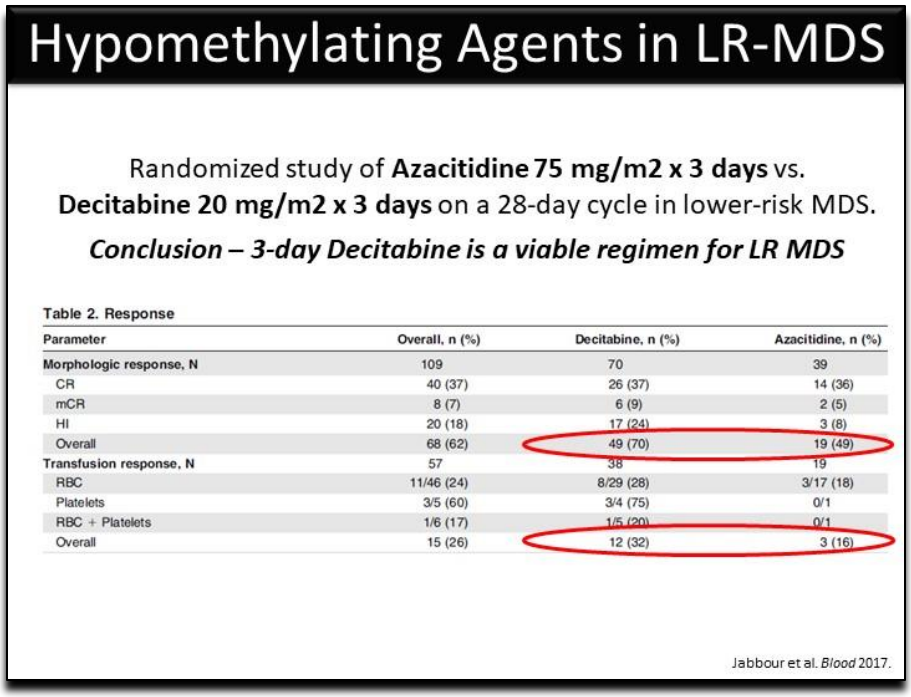
Now, I will say that the approval might be kind of narrow because the study that was done, particularly in patients who had a form of MDS called MDS with ring sideroblast. And a broader study to look at this in more MDS patients is currently underway.



Platelet Growth Factors

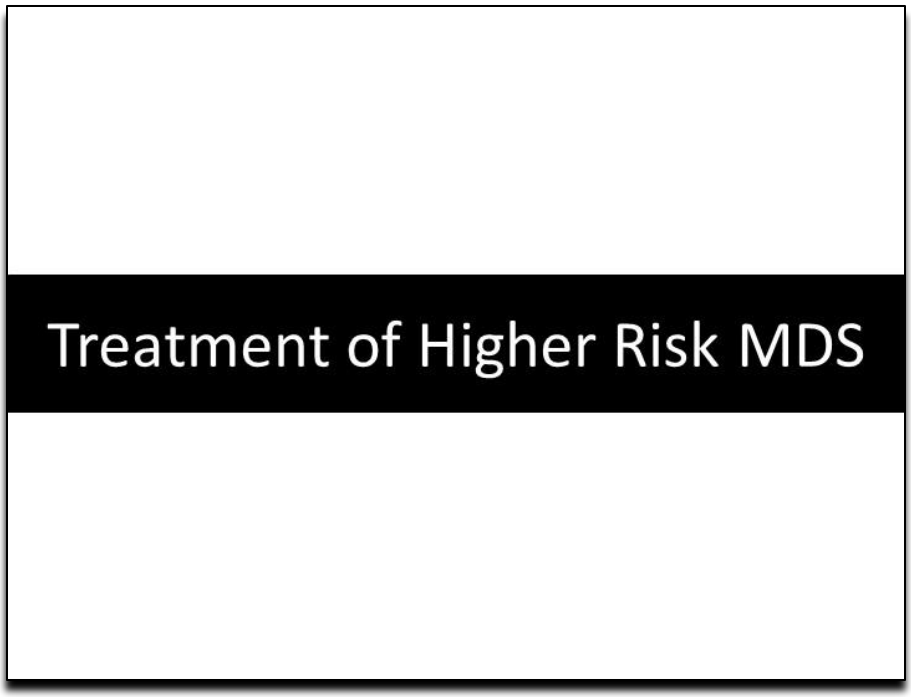
Finally, I want to talk about platelet growth factors. These are similar to the erythropoiesis-stimulating agents but they act on platelet precursors. Several of these are available because they were approved in other conditions for low platelets. And we have used them in MDS in patients whose primary problem is having a low platelet count.

It looks like these drugs are fairly safe in lower risk MDS. However, we need to be careful with our use in higher risk MDS, as it might actually stimulate the production of blasts and make it look like a patient has more accelerated disease than they do.



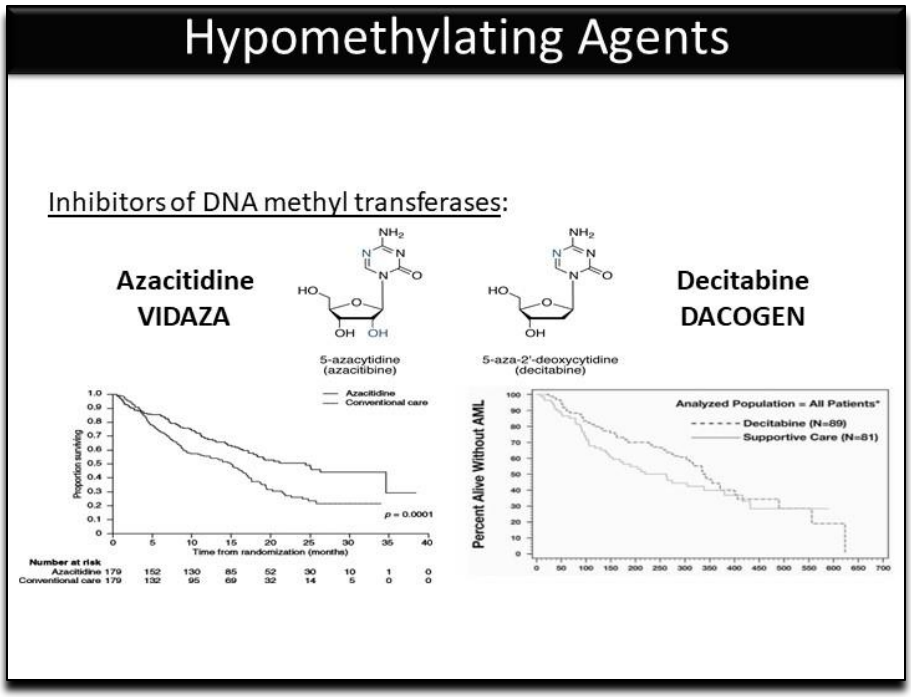
Hypomethylating Agents in LR-MDS

Finally, one option that we're starting to see more of, particularly in the U.S., is the use of drugs like azacitidine (Vidaza®) or decitabine (Dacogen®). These are what we call hypomethylating agents that we typically use in higher risk MDS. We're starting to use them in lower risk MDS patients, often at a reduced dose or a more tolerable schedule. And we see response rates that are quite favorable. We see response rates that are approaching 40% or 50%, including patients that become transfusion independent with these agents.



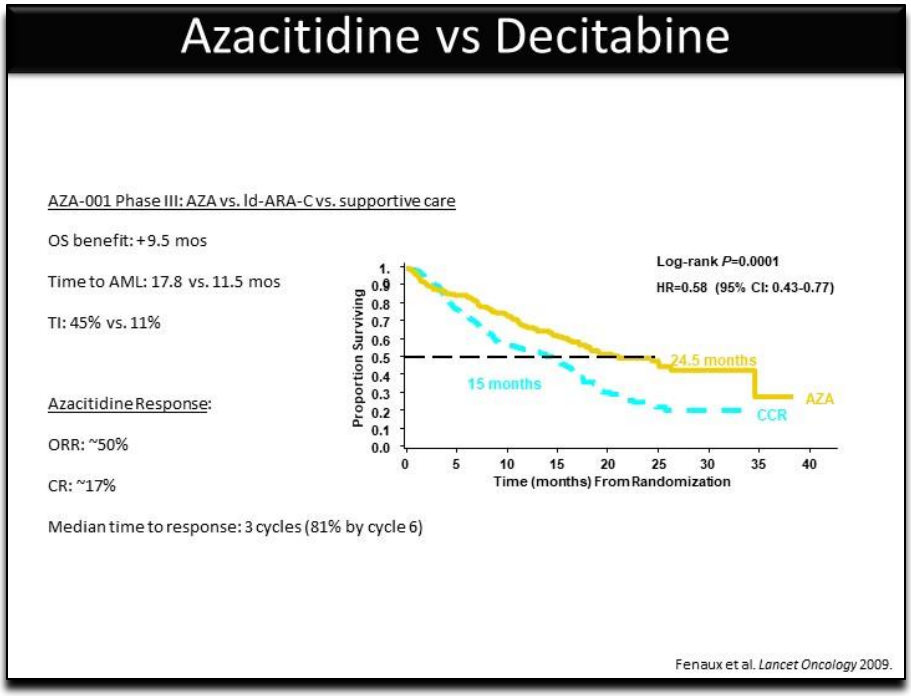
Treatment of Higher Risk MDS

So now, I want to change gears and talk about treatment of higher risk MDS. So, higher risk MDS, as I told you before, are patients who have more aggressive disease. It is more likely to turn into acute leukemia. So, here our focus is a little bit different. We are willing to tolerate some side effects of the medication—some difficulty with treatment—in order to help control the disease and extend life.



Hypomethylating Agents

The two major drugs that are currently approved for higher risk MDS are azacitidine (Vidaza®) and decitabine (Dacogen®). Both of these, as you can see here by their molecular structure, are very similar drugs. And in fact, azacitidine (Vidaza®) is partially converted into decitabine (Dacogen®) in the body.



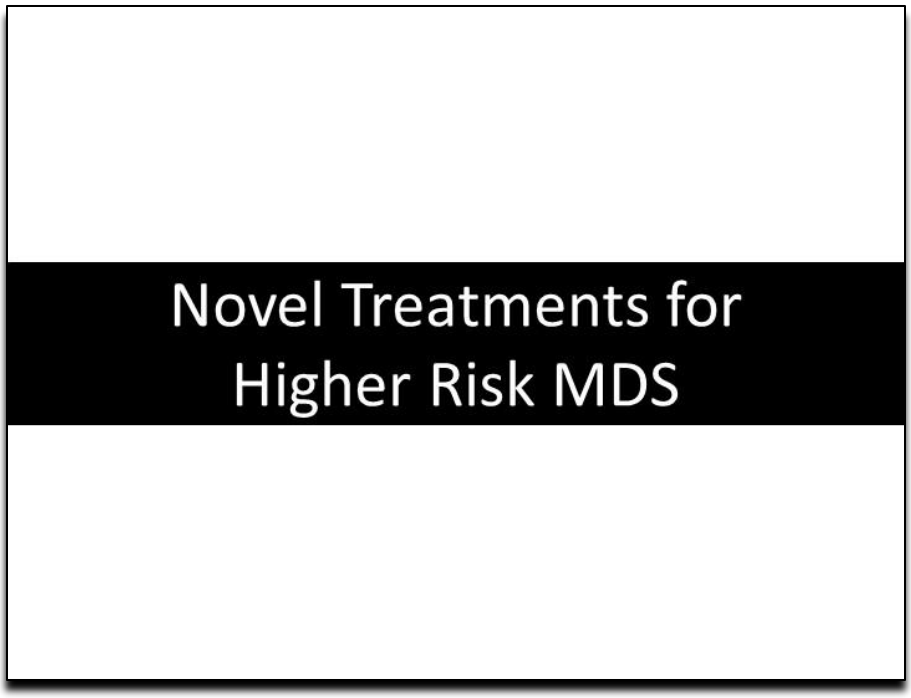
Azacitidine (Vidaza®) vs Decitabine (Dacogen®)

However, we have data that suggests that azacitidine (Vidaza®) does prolong life in patients who are treated. This is from a clinical study done in 2001 and published about 10 years ago. It shows that

about 45% of patients who are treated with this drug will respond and that the treated population has a life expectancy that's about 9 months longer than patients who got the best supportive care.

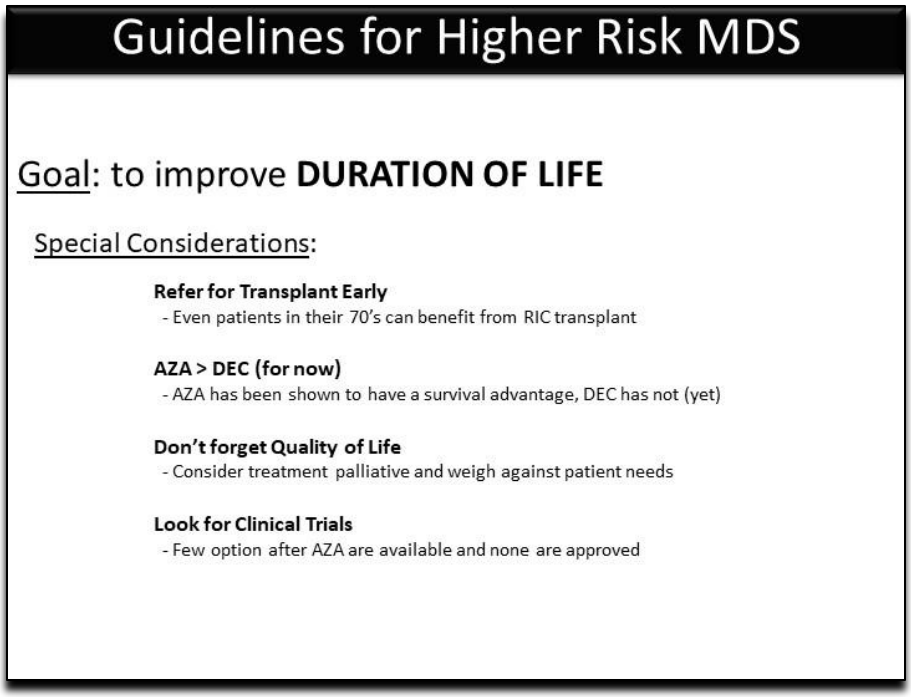
Only about 17% of patients will have what we call a complete response. And I want to make the difference here. Patients who get improvement may see improvement in their blood counts. A complete response means that when we look at their bone marrow, we see that their blasts have gone away and their blood counts have improved. So how a complete response is presumed to be the best kind of response. And I'll show you why that's important when we talk about some novel therapies that seem to have better complete response rates than azacitidine (Vidaza®) alone.

So, one thing that I'm glossing over here that I can help address in questions if you have is that one of the major treatments for MDS is a stem cell or a bone marrow transplant. I don't have time on this call to go into great details about that, but for any patient with higher risk MDS who is a good candidate for a transplant, I highly recommend that they meet with a transplant physician to discuss those options as that is the only potential cure for MDS. All the other therapies that we're talking about today help control the disease or help improve how patients feel while having this disease but don't necessarily cure it.



Novel Treatments for Higher Risk MDS

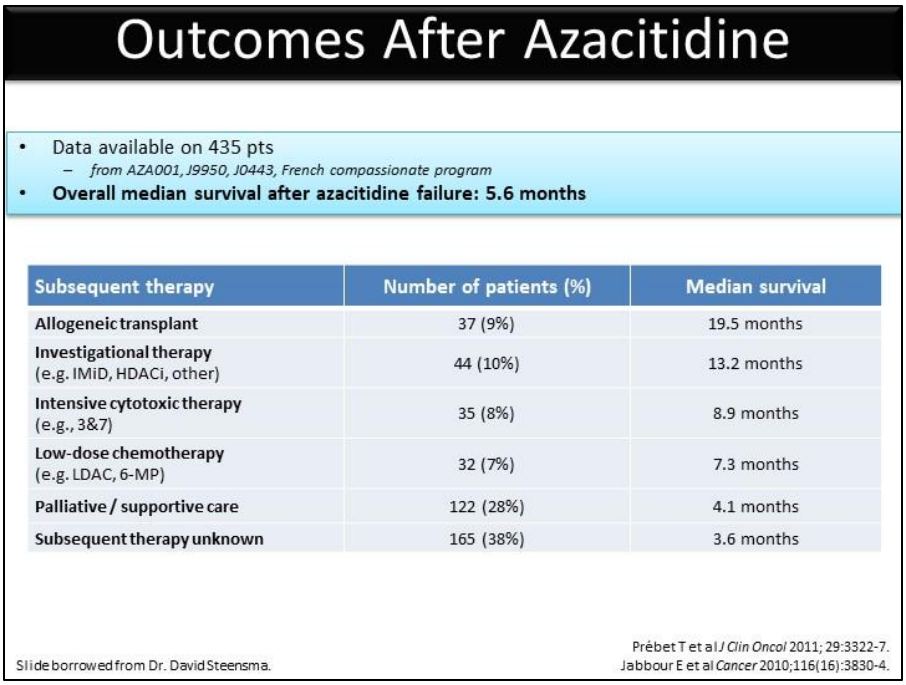
What I want to focus on now are novel therapies besides transplant that are on the horizon for patients with MDS.



Guidelines for Higher Risk MDS

So, my general approach today is focusing on duration of life in patients with MDS, where I refer them for transplant early, particularly if they are younger—and that can include patients that are even in their early 70s—treatment with azacitidine (Vidaza®) if transplant is not an option or even sometimes if it is, and then looking for clinical trials.

What I want to talk about is why we need these clinical studies. It turns out that if patients get treated with drugs like azacitidine (Vidaza®), only about half of them respond. Their responses take a long time to occur and the responses are not particularly durable—lasting only a few months to a year or two.

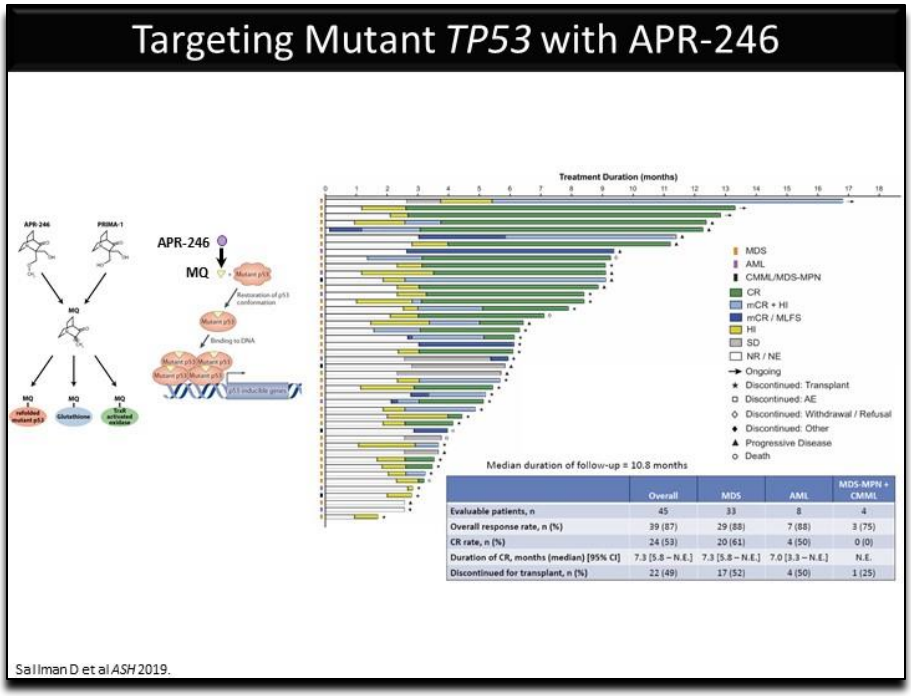


Outcomes After Azacitidine (Vidaza®)

Outcomes after azacitidine (Vidaza®) has been tried and no longer works for the patient aren't great. Most patients will have to go onto some other therapy. Sometimes other therapies are not particularly effective. And you can see that the median survival after treatment with one of these other options isn't great. On average, the life expectancy is about 6 months after azacitidine (Vidaza®) stops working for patients.

Treatment of Higher Risk MDS

So, the short answer here is that we need better therapies, and we need more therapies—more options.



Targeting Mutant *TP53* with APR-246

As I mentioned earlier in the call, one of the worst players in MDS are mutations in this gene called *TP53*. *TP53* turns out to be a very important gene. It encodes a protein that is responsible for arresting cells that have suffered a lot of damage, and these mutated cells in MDS have suffered a lot of \

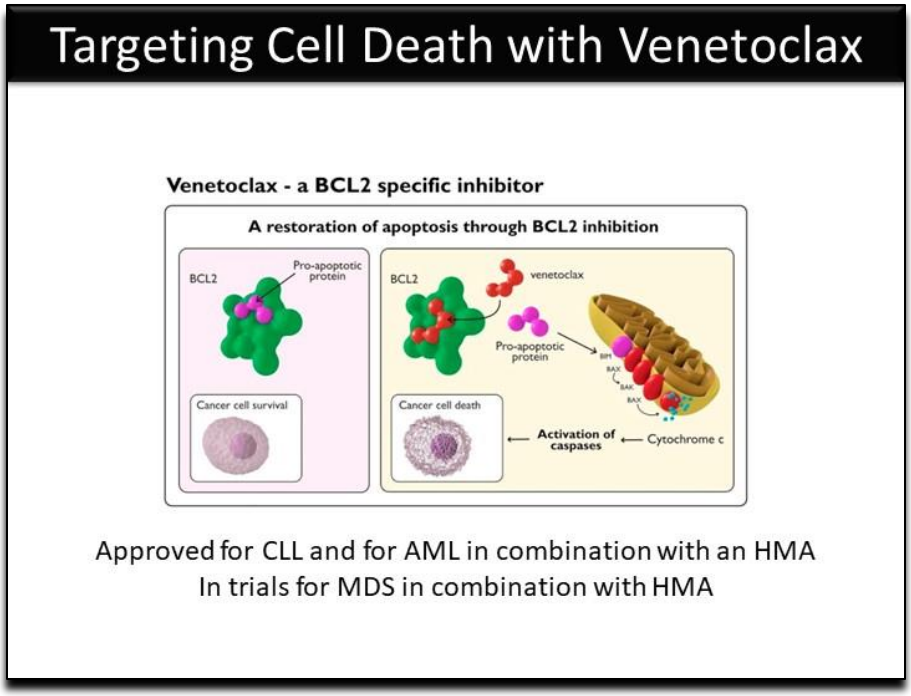
damage. If this protein is broken, these cells don't stop when they should. And they continue to grow in an uncontrolled manner.

So, several companies have looked at ways to try to stabilize or return the function of mutated *TP53*. And one of the drugs that appears to have this capability is a drug called APR-246. So, what they do is they take patients that have MDS or AML—acute myeloid leukemia—with mutations in *TP53*. They treat them with this medication that in the body binds the *TP53*, intends to stabilize it, and prevents it from working in an abnormal manner—hopefully restoring its function.

And results of this study that were recently updated at the American Society of Hematology meeting just last week are very promising. They show that response rates are quite high. Overall response rates were actually in the 80% range for both MDS and the handful of patients with AML that were treated.

And these responses appear to be somewhat durable in many patients. As shown in this bar graph here, patients in green had a complete response. Again, this is the best kind of response where not only the bone marrow leukemia-like cells go down—the blast cells go down—but the blood counts improve as well.

Now, we don't have a lot of long-term follow-up, so we don't necessarily know how long the therapy is going to work. But the fact that it works fairly well when you combine it with a hypomethylating agent, as was done in the study, is very encouraging.



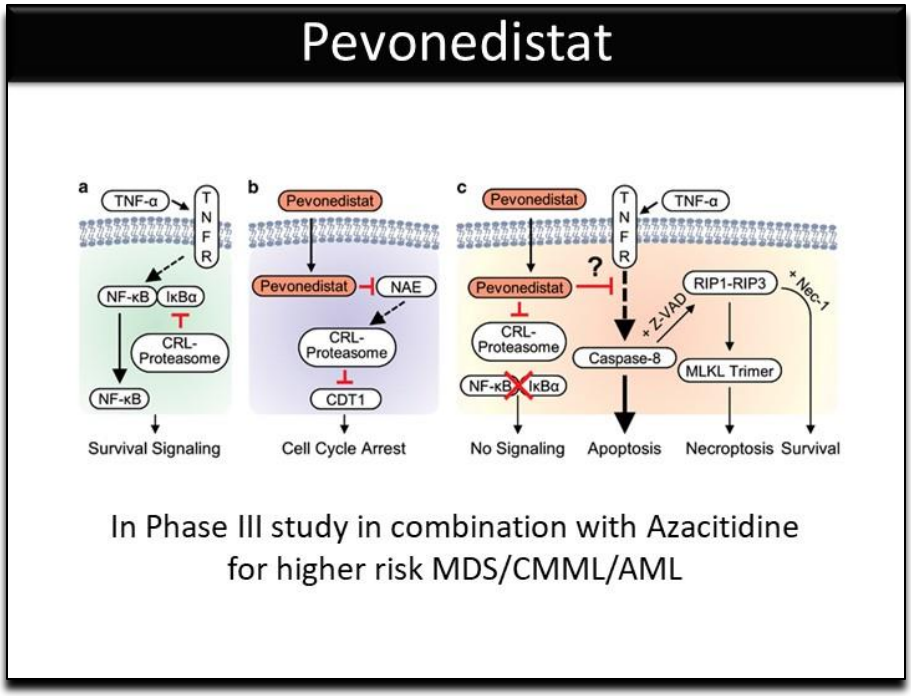
Targeting Cell Death with Venetoclax (Venclexta®)

Another therapy I want to mention is a drug that is actually already approved for patients with acute myeloid leukemia, and this drug is called venetoclax (Venclexta®). And like *TP53*, venetoclax (Venclexta®) targets cell death pathways. Under normal circumstances, normal cells will recognize when they have suffered some sort of DNA damage or other insult and essentially commit suicide to avoid becoming a problem.

Cancer cells have shut off this suicide mechanism, and they tend to not undergo normal cell death when they should. And this drug venetoclax (Venclexta®) helps restore that function. So when treated,

these cells suddenly recognize that they are highly abnormal and will commit suicide, particularly if we have another agent that is helping work with the venetoclax (Venclexta®).

The studies of combinations of decitabine (Dacogen®) or azacitidine (Vidaza®) with venetoclax (Venclexta®) in MDS are ongoing and, as I mentioned, have already been approved in patients with acute myeloid leukemia. So, this is an option that is theoretically available to physicians today.

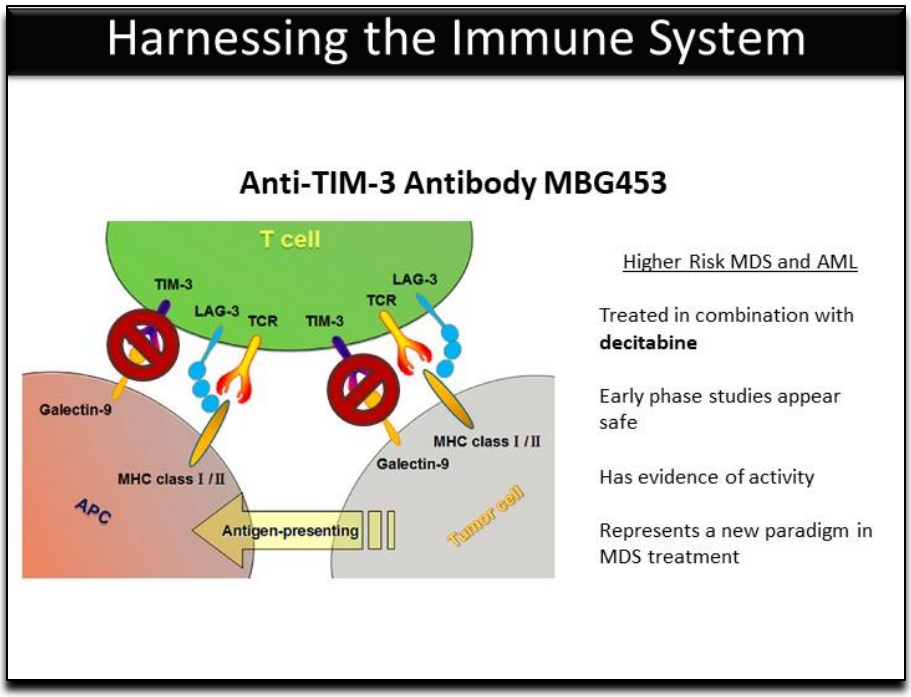


Pevonedistat

Another study that I think is far along in development is a study looking at a novel agent called pevonedistat. Pevonedistat, in combination with azacitidine (Vidaza®), has now been tested in a Phase III study that recently was close to accrual. We're still awaiting the results of this study in the earlier phase II study, which I hope are reported in this next coming year.

The idea behind this drug is that it blocks many of the cell growth pathways that MDS cells use to grow and expand and out-compete their normal counterparts. And we hope by targeting this pathway, we slow down the progression of the disease and can help the body fight it back.

Hopefully we'll hear positive results in the coming year.

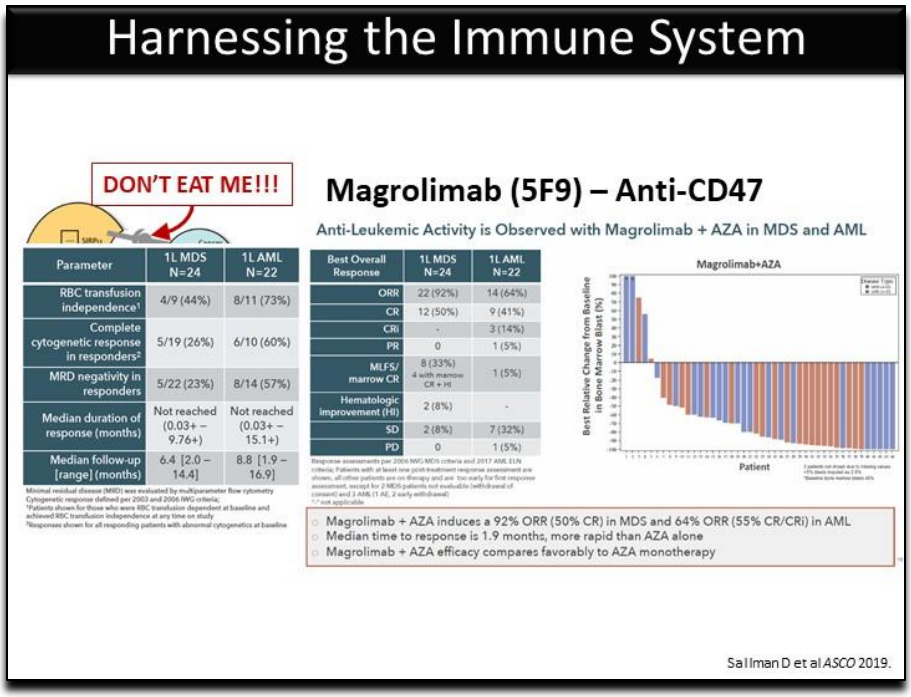


Harnessing the Immune System

One of the newest therapies that I think is now being recognized is immune-based therapies. So, one particular kind of immune-based therapy focuses on connections between T cells that are part of our immune system and tumor cells and the antigen-presenting cells that help stimulate the immune cells. I want you to focus on a receptor called TIM-3, T-I-M-3. This is a receptor that sits next to the P cell receptor and sends signals to the T cell. If TIM-3 is engaged—if it's turned on—it actually tells the T cell to back off—to become what we call senescent or anergic, in other words, and stop working. So, it's a negative feedback signal.

What this drug, MBG453, does is it binds to that TIM-3 protein, and it prevents it from acting normally. So now, when a T cell engages with a tumor cell that's trying to fool it by showing activation of TIM-3, that signal is blocked, and the tumor cell is now recognized as being something the T cell should attack and engage--and hopefully leading to a good outcome.

Early data presented at the American Society of Hematology Meeting, in combination with decitabine (Dacogen®), suggested that this drug is relatively safe and has evidence of activity. And it really represents a completely new paradigm in MDS treatment—one focusing on harnessing the immune system.



Harnessing the Immune System

Another drug that harnesses the immune system does it in a very different way. This is a drug called magrolimab, or 5F9. This is an anti-CD47 drug, also an antibody, just like the prior one. And it recognizes that tumor cells, shown here, normally express an eat-me signal. There's something wrong with them, and the immune system can recognize that.

Now, the really smart tumor cells also put up a don't-eat-me signal that says, "No, actually I'm a normal cell, leave me alone!" And when immune cells come to check the cell out to see if it's something that should be dealt with, they get that don't-eat-me signal and ignore the tumor cell.

And in this particular case, the effector cell is not a T cell. The effector cell here is probably a macrophage or a monocyte whose job it is to engulf the abnormal cells and digest them. What this drug does is it blocks that don't-eat-me signal so that the only signal that's left is that eat-me signal. And that helps engage the macrophage to recognize the tumor cell and consume it.

In another study where they combined this magrolimab with a hypomethylating agent, like azacitidine (Vidaza®), they showed some pretty remarkable results. In early phase studies, the response in MDS patients, only 24 patients said the response was quite good; 22 out of the 24 patients had an objective response.

And 50% of the patients had what we call a complete response—again where not only the bone marrow looks better, but the blood counts do as well. And on the bar chart shown on the right, you can see the reduction in blast counts in the bone marrow with patients in blue having MDS and patients in red having AML.

And you can see that the majority of patients that were treated with this combination showed a significant reduction in their blast counts. Now again, these are early phase studies and we don't yet understand what the duration of response is likely to be. But they represent a completely new paradigm in how we treat MDS and are very exciting to us, looking forward.

Acknowledgments

So with that, I want to make sure that I leave enough time for questions. I'll go ahead and wrap up. I'll acknowledge the folks who work with me at my home institution and The Leukemia & Lymphoma Society, for helping put this on and supporting us both in the research and the clinical area.

Questions

And I will be happy to take any questions.

Ms. Lizette Figueroa-Rivera
Thank you, Dr. Bejar, for your very informative presentation. It's now time for the question-and-answer portion of our program.

And we'll take the first question from our web audience. Doctor, Shelly is asking, "How close are we to CAR [T-cell] therapy for MDS patients, and how about the use of CRISPR technology?"

Rafael Bejar, MD, PhD
Both are great questions. So, CAR [T-cell] therapy is when we take a person's own T cells and genetically modify them, so now variant cells recognize the targets that we want them to recognize. This has been very effective in a different kind of blood cancer called lymphoma and lymphoid leukemia.

We don't yet have FDA-approved CAR T-cell therapies in MDS or AML, in part because these are more difficult to target. We need to target something that the body doesn't need normally. And at the moment, many of the targets that are particularly effective in diseases like MDS are also on normal cells.

So, these are being investigated in clinical studies now. I think it's going to be a little bit more challenging to get these drugs approved in MDS and AML—or at least to be effective and safe—than it was for some of these other disorders. But I think they will be in our future.

Now, CRISPR is a DNA-editing technique that we can use to change the DNA of cells in ways that might favor a response to disease. And there's a variety of ways that this could be done. It could actually be combined with CAR T-cell therapy to help put in the receptors that we want those T cells to have in a more efficient manner.

But there are other options that are being looked at as well—maybe using CRISPR to help put in proteins that might act as a vaccine for the disease, and so on. So, I'm very excited to see how these two technologies carry us into the future.

Ms. Lizette Figueroa-Rivera
Thank you. And we'll take the next question from our telephone audience, please.

Operator
A phone question comes from Karen calling from New York. Please state your question.

Karen
Yes, I do. I was told I had low MDS. I'm getting 40,000 of Procrit® (epoetin) twice a week and Zarxio® 3,000 twice a week. Can you tell me a little bit about that?

Rafael Bejar, MD, PhD
Sure. I'm glad you asked that question. As I mentioned earlier in the talk—that we can use erythropoiesis-stimulating agents to help boost red blood cell production. One of the things that we can do is combine that with a white blood cell growth factor. In this case you mentioned Zarxio® . Another name for that would be Neupogen® (filgrastim), or GCSF (.granulocyte-colony stimulating factor).

Karen
Yes.

Rafael Bejar, MD, PhD
And together they seem to be slightly more effective. So, in my practice I will start a patient on a red blood cell growth factor, like Procrit® (epoetin) [and] see if they respond. And if they don't have a great response or don't respond to the extent that I would like them to, I will sometimes add a drug like Zarxio® or GCSF to help boost that response, which is effective in about 26% or 27% of cases.

Ms. Lizette Figueroa-Rivera
And thank you for the question. The next question comes from Joy. Joy is asking if there's any other next steps. She was diagnosed in June, is getting weekly transfusions because of low hemoglobin, and does receive Procrit® (epoetin) weekly. And she can't tolerate Revlimid® (lenalidomide). So, any ideas for any next steps?

Rafael Bejar, MD, PhD
Right. As I mentioned, we have increasing options now in patients with lower risk MDS. I recommend that you reach out to an MDS center of excellence and see if there are clinical trials in your area that might be effective. And as I mentioned, if we get this drug luspatercept (Reblozyl®) approved, it might be an effective option for some patients with lower risk MDS who have not responded as effectively as we would hope to drugs like the ESAs, the erythropoiesis-stimulating agents.

Operator
Our next question comes from Mary Ellen calling from Pennsylvania. Please state your question.

Mary Ellen
Yes, I have MDS minus 5q, and I think, I understand that's low. It's very low. I'm on Revlimid® (lenalidomide). What is your opinion of the Revlimid® (lenalidomide) medicine?

Rafael Bejar, MD, PhD
As I mentioned in the talk, Revlimid® (lenalidomide) is one of our most effective medications in patients like you who have deletion of chromosome 5q. It's the first therapy that I would consider for a lower risk MDS patient.

Ms. Lizette Figueroa-Rivera
Thank you. The next question comes from Leigh. Leigh is asking, "Is the IPSS-R used after initial diagnosis, or is it only a benefit at the time of diagnosis?"

Rafael Bejar, MD, PhD
That's a great question. So, the IPSS-R was designed by looking at people who were newly diagnosed. However, since then we have looked at a variety of different populations of patients—some of whom were evaluated after diagnosis, some of whom were evaluated even after treatment. And we see that the IPSS-R is still valid, even in those patient populations.

So, I do use it as a dynamic scoring system. In other words, I use it at the time of diagnosis. And if there's a significant change along the way—there's evolution of disease or response after treatment—we can use the IPSS-R as a guide. It may not be as accurate in those situations, but I do think it's still useful to help us understand what is happening to our patients over time.

Ms. Lizette Figueroa-Rivera
Thank you and we'll take the next question from the telephone audience, please.

Operator
Thank you. Our next question comes from Agnes calling from Arizona. Please state your question.

Agnes
I was wondering—I was diagnosed 17 years ago. And it is starting to escalate at this time. I also have stage 4 kidney and heart disease and all kinds of complications. What is the longevity of this, of life at this time?

Rafael Bejar, MD, PhD
I understand what you're asking. This is a question that I often get in clinic as well, and the fact is that MDS at any stage probably does affect life expectancy to some degree. However, the risk is really

important. A person that has had MDS for more than 10 or 15 years likely has a very slowly progressive form of this disease, and it may not be the most important factor in their health.

So, for the patients like that, I tell them to focus more on the other medical problems that they have while we continue to support them from the MDS standpoint, but that ultimately the MDS is unlikely to be the major concern that they would have, going forward.

Ms. Lizette Figueroa-Rivera
Thank you. And the next question comes from Roselle. Roselle is asking about the side effects of venetoclax (Venclexta®).

Rafael Bejar, MD, PhD
A very good question. I didn't go into that in the talk, but venetoclax (Venclexta®) is a very well-tolerated drug. It doesn't seem to have a lot of immediate side effects in the form of nausea or vomiting or rash or anything like that. But one of the major things that it does is it does suppress the bone marrow function, so it actually lowers blood counts initially. And in particular, it lowers white blood cell counts or neutrophil counts quite substantially.

I think we're still learning how to use this drug in MDS. It was approved for AML, where the disease tends to be very aggressive. And we were willing to tolerate having low neutrophil counts in order to treat that disease. But in MDS the situation might be different.

So, we're very wary of the fact that this drug lowers white blood cell counts and can make people more prone to infection. And we often take steps to help prevent those infections in the form of preventative antibiotics or breaks from treatment or so on to help recover the neutrophil count. And I'm glad that we're doing clinical trials with that drug in MDS so we can better understand how to use it in that context.

Ms. Lizette Figueroa-Rivera
Thank you. And our next question comes from Joyce. What is the success rate in using decitabine (Dacogen®) with eltrombopag (Promacta®)?

Rafael Bejar, MD, PhD
Another good question. So, let me define those two things. So, eltrombopag (Promacta®) is a pill that increases platelet counts in patients who have low platelets. It stimulates that platelet production receptor. And decitabine (Dacogen®) is one of the hypomethylating agents, like azacitidine (Vidaza®). Now, these have been studied in conjunction—together—in patients who have higher risk MDS.

And unfortunately, the outcomes with the combination were actually worse than without the eltrombopag (Promacta®), so with azacitidine (Vidaza®) alone. We think that they actually make the bone marrow more susceptible to the toxic effects of the drug. So, we actually don't recommend combining eltrombopag (Promacta®) and a hypomethylating agent together in patients with higher risk disease.

Ms. Lizette Figueroa-Rivera
Thank you. And we'll take the next question from the telephone audience, please.

Operator
Our next question comes from Debra calling from Ohio. Please state your question.

Debra
Hi. I had high-grade MDS in 2017. I had a stem cell transplant and then I had a boost. And the doctor has me on Jakafi® (ruxolitinib) because I had host-versus-graft and was in the hospital for several months with complications, but I'm cancer-free now. And I was just wondering if you had ever heard of using the Jakafi® (ruxolitinib) for the host-versus-graft?

Rafael Bejar, MD, PhD
Right. So, Jakafi® (ruxolitinib) is a drug that we typically don't think of as an MDS therapy. It's a drug that has been used in a related disease called myelofibrosis. However, one of the effects that it has is it tends to quell or suppress the immune system to some extent. So, it actually has been approved for the use in patients who have graft-versus-host disease as a means to try to make that better.

And like I said, it is not being used for the MDS in this case. It's really being used to treat the immune system to ameliorate or make better those graft-versus-host effects. This is something that we are starting to do more and more often.

Ms. Lizette Figueroa-Rivera
Thank you. And our next question from the Web comes from Jen. She is asking, "How are MDS centers of excellence identified?"

Rafael Bejar, MD, PhD
Good question. So, there are a couple of mechanisms for that. I think The Leukemia & Lymphoma Society has a list of experts in your area that might be helpful. The MDS Foundation formally recognizes MDS centers of excellence around the world. And they require that centers not only have patients—or not only have doctors that are focused on MDS—but that also have all the other resources that a patient with MDS might need, including expert pathologists that help diagnose the disease, clinical studies or clinical trials, and research into MDS at that site. So, we truly identify centers where we have everything that a patient might need and expertise and cutting-edge treatments for the disease.

Ms. Lizette Figueroa-Rivera
Thank you. And Enrique is asking, "Does MDS always progress to leukemia?"

Rafael Bejar, MD, PhD
Another great question. So, actually MDS does not always progress to leukemia. In fact, it's only about one-third of patients that will have leukemia after MDS. Patients with higher risk disease—patients who start with more leukemia-like cells in the bone marrow—have a greater risk. Whereas patients who have lower risk disease, who don't have those bone marrow blasts, they tend to have a very low rate of progression of leukemia—about 10% or 15%.

So, unfortunately—well fortunately, I would say—most patients don't develop leukemia. But unfortunately, even if patients don't develop leukemia, MDS still can still be a very severe and often fatal disease.

Ms. Lizette Figueroa-Rivera
Thank you. And along that line, Clark is asking, "Is a patient who transforms to AML after MDS treated differently than a patient who is diagnosed with de novo AML?"

Rafael Bejar, MD, PhD
Great question. So, it depends on a variety of factors. And it depends in part on the patient's age and what other medical problems they have at the time. If they are younger or more fit, then we may treat them very differently. We may treat them more like a de novo AML patient who didn't have MDS before that.

And they might get aggressive chemotherapy and be referred for stem cell transplantation, whereas older patients who develop AML after MDS might be treated with some of the same drugs that we use to treat MDS. They might be treated with hypomethylating agents. They might be treated with some of these new combinations that I mentioned were approved—like for example, the combination of venetoclax (Venclexta®).

Ms. Lizette Figueroa-Rivera
Thank you. And we'll take the next question from our telephone audience, please.

Operator
Our next question comes from Marsha calling from North Carolina. Please state your question.

Marsha
Hi, Dr. Bejar. Thank you for taking my question. My 86-year-old mother has level 2 as far as her rating for risk. She is transfusion-dependent. She had tried Vidaza® (azacitidine) for about 6 months, could not tolerate it. She also was on Aranesp® (darbepoetin) injections and they apparently have not done any good.

You mentioned a drug—I couldn't catch the name of it—that started with an "L" which is being used for some other conditions. And she also has the ring sideroblast and is not expected to live very much longer. Would that be a drug that might be considered for her now, and what are the side effects of it?

Rafael Bejar, MD, PhD
Thanks for that question. So, the drug that I mentioned has a long name called luspatercept (Reblozyl®). And it is recently approved for another blood condition called beta thalassemia. But the Phase III clinical trial for patients who have ring sideroblast, just like you described your mother having, that clinical trial looked very favorable.

I suspect that the drug will be approved in the near future—I'm not exactly sure when that will be—for MDS. But that would be an option that I would consider for patients who have tried other things to increase their hemoglobin and not been successful in doing so.

Ms. Lizette Figueroa-Rivera
Thank you. And our last question today comes from Linda. She says, "Both of my children were diagnosed with MDS when they were in their early 20s. They have both undergone transplants. And it was discovered that their father is the carrier of a *GATA2* gene mutation, which was discovered in both of them and considered the cause of them having MDS at such a young age."

Their father is now 55 years old and yet shows no signs of MDS and goes for blood tests regularly. Basically, she is just asking, "What are the odds that he'll develop MDS? Or could he just be a carrier of this gene mutation and never develop the disease?"

Rafael Bejar, MD, PhD
That's a great question. I think we could even dedicate a whole hour to simply talking about that kind of concept. So, one of the things that we learned is that many people who have MDS and don't have a family history might actually have something they were born with that predisposed them to get it in the first place.

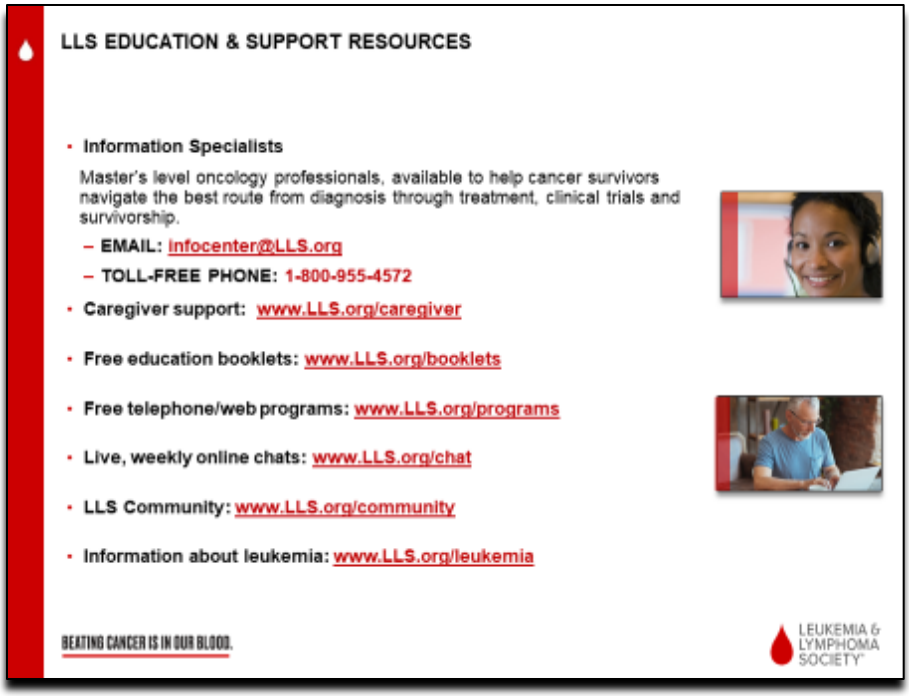
And the reason that they don't have a family history is that that disease may be variably penetrated. It may not occur in everyone who is a carrier. In some examples, we see families where the disease occurs earlier and earlier in every subsequent generation, so that situations like the one you describe occur—where the parent who is a carrier has the gene but doesn't necessarily have the disease.

We don't really understand what drives those differences. But we know that the disease can manifest in different ways in different people, even if they have the same exact genetic mutation.

Now, *GATA2* we think of as being fairly penetrant, meaning that most people who have a typical mutation in this gene will have some manifestation of disease, even if they don't necessarily progress to having MDS. So unfortunately, I can't answer the question with regard to that individual, to the father in this example. But I will say that it's not unusual, as we're learning more and more about these conditions, to find that some people are carriers and don't necessarily ever develop the disease.

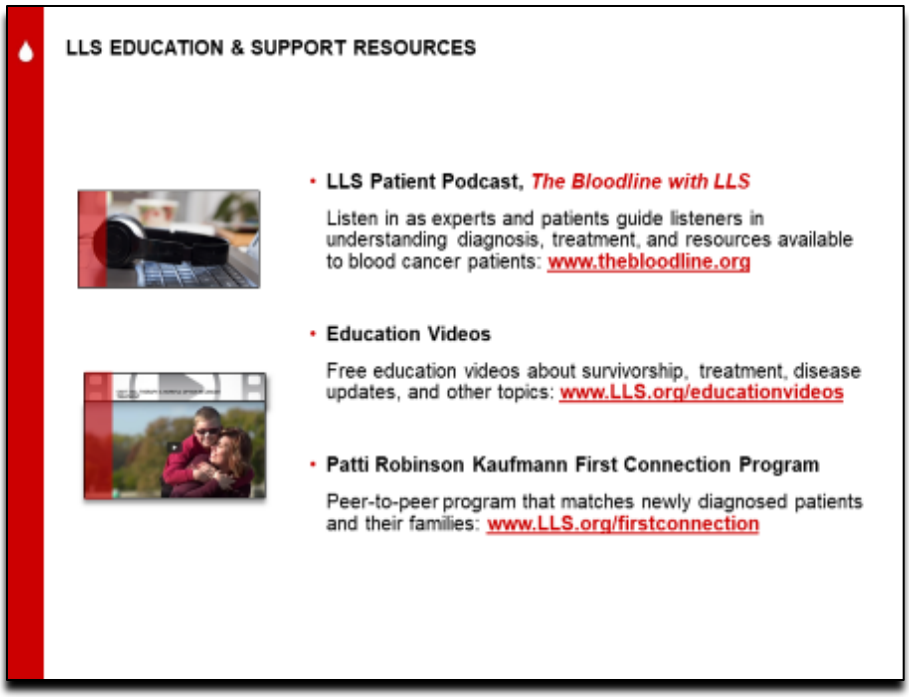
Ms. Lizette Figueroa-Rivera
Thank you. Thank you, Linda, for your question, which was our last question of the day. And special thanks to Dr. Bejar for sharing his expertise with us and for his continued dedication to our blood cancer patients. Thank you so much, doctor.

Rafael Bejar, MD, PhD
Thanks for having me.



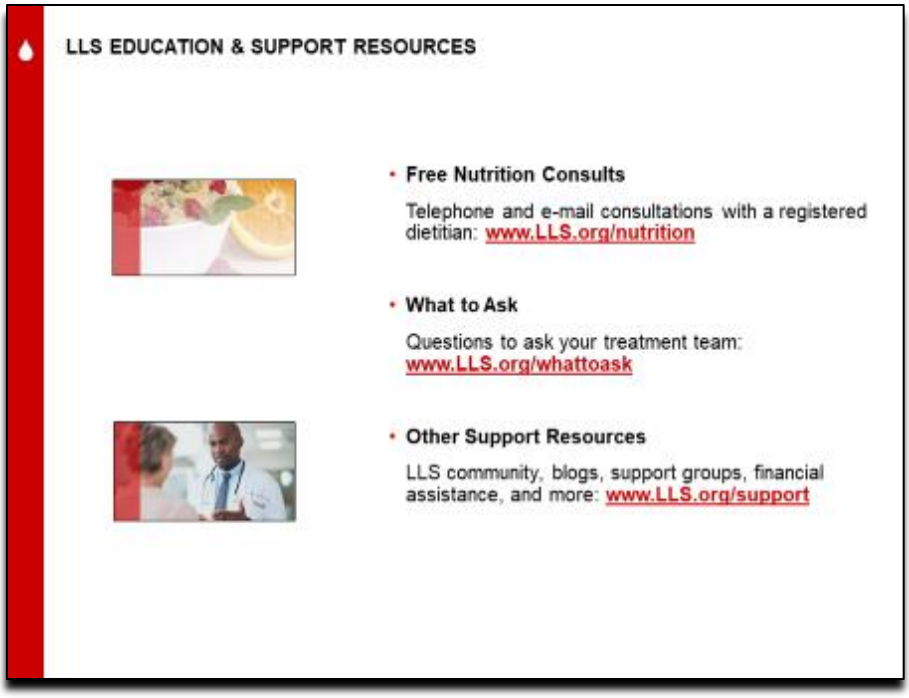
LLS Education & Support Resources

Ms. Lizette Figueroa-Rivera
Sure, thank you. If we weren't able to get to your question today, please contact an Information Specialist at The Leukemia & Lymphoma Society at 1-800-955-4572 from 9 AM to 9 PM Eastern time or reach us by e-mail at *infocenter@lls.org*. Information Specialists are available to answer your questions about treatment, including clinical trials, or answer other questions you may have about support, including financial assistance for treatment. We could also guide you to those centers of excellence.



LLS Education & Support Resources

Again, we would like to acknowledge and thank Bristol-Myers Squibb and Takeda Oncology for support of this program.



LLS Education & Support Resources

Dr. Bejar, thank you again for volunteering your time with us today. On behalf of The Leukemia & Lymphoma Society, thank you all for joining this program.

Thank You!

We hope you will join us in the future as we keep you up to date on the latest advancements for MDS. Take good care.